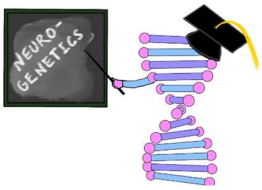


Teaching Guide

Module 8: Stroke

Slide 1: Introduce the phenotype for this module.

Slide 2: Objectives, from text on slide.

Slide 3: **Disclose the chief complaint.** Here instead of saying abnormal eye movements, we are already clarifying a phenotype with the goal of eliciting a focused differential.

Slide 4: Spend a few minutes having participants share genetic causes of stroke based on their previous knowledge. For example, if they say MELAS, encourage them to share what additional information they know about the condition *including gene, inheritance pattern, MRI pattern, treatment etc.*

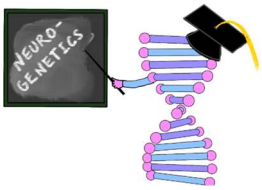
Slide 5- 6: This is course material where instructor will be helping participants form some concepts in genetic causes of stroke. *Acknowledge this is a busy slide and clarify participants are not expected to remember all the genes.* But as they encounter more cases in practice, they will automatically start remembering more about these conditions. Genetic causes of stroke can be categorized under 4 broad categories –

1. **Disorders of connective tissue affecting vasculature**
2. **Metabolic and mitochondrial disorders**
3. **Disorders of coagulation**
4. **Other miscellaneous conditions.**

Age of first stroke, MRI pattern and type of vessel involvement can provide clues. Mention CADASIL which is an autosomal dominant condition and presents with migraine, memory issue, TIA and stroke in 30-40s. Mention MELAS which is a maternally inherited mitochondrial disease, DWI changes do not follow any particular vascular territory (usually asymmetric in parieto-occipital lobes), hence the term 'stroke-like'. Disorders of coagulation are caused by mutations in genes of coagulation pathway. Usually, it is a part of work-up in young stroke and hematology (rather than neurology or genetics) is involved. The facilitator may choose to elaborate on any other entity mentioned in these slides based on personal knowledge and experience.

Slide 7: Text from slide.

Slide 8: this is the first MRI at presentation at age 6.



Slide 9: On conventional angio, there was suggestion of **dynamic artery compression**. So angio was repeated with formal head rotation, demonstrating artery compression. Note that she was diagnosed with Bow Hunter syndrome and underwent cervical fusion. Dynamic vertebral artery compression, more commonly known as Bow Hunter's syndrome in adults, is caused by mechanical pressure or stenosis of the vertebral artery during neck rotation from external structures, such as osteophytes, disc herniation, or bands of tissue or tumors, and leads to vertebrobasilar insufficiency. It presents with transient ischemic attacks and posterior circulation strokes which are thought to be a result of endothelial damage due to repetitive shear stress. It is not a genetic/monogenic condition.

Slide 10: Repeat infarction happened 2 weeks after cervical fusion. Discharged home.

Slide 11: Another 2 weeks later, came back to hospital (for a third time), with subarachnoid hemorrhage and hydrocephalus. **Since the patient continued to have strokes despite the cervical fusion, the additional history of recurrent fevers, and the hemorrhage, there was stronger suspicion for a genetic etiology**, and this is supported by the family history seen in the next slide.

Slide 12-13:

- *What could be the possible mode of inheritance*?

  Answer – autosomal recessive (given consanguinity, as denoted by double lines between parents who are first cousins)

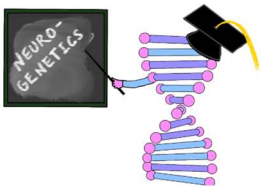
- *If confirmed to have a genetic condition, what would be the estimated recurrence rates in future pregnancies?*

  Answer – 25% changes of being affected, 50% to be unaffected but carriers like parents, 25% chance of being unaffected and not carriers.

Slide 14-15: Characteristics of autosomal recessive pedigree, text from slide. Discuss co-efficient of inbreeding. The **degree of consanguinity determines what portion of the genome could be affected by loss of heterozygosity**, thereby raising risk for AR disorders.

Slide 16-20: (Common for several modules. Depending on which module is being done, may or may not repeat all the information)

- Central Dogma developed by Francis Crick is a theory stating that genetic information flows only in one direction, from DNA, to RNA, to protein, or RNA directly to protein.
- **When there is variation or mutation or spelling error in the underlying sequence of the gene, that leads to genetic disorders**. These mutations can be inherited or de novo. In



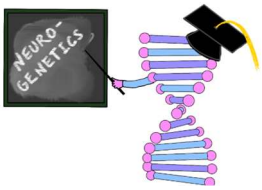
some cases, spelling errors are needed in both alleles to produce a defect in the protein, these are known as recessive disorder. Whereas in some cases, one variant in one of the alleles is sufficient to cause a genetic disorder referred to as dominant conditions.

- When analysis of a patient's genes shows a variant, but it is unclear whether the variant is related to the patient's medical condition, it is classified as a variant of uncertain significance (abbreviated as VUS). In many cases, these variants are so rare in the population that little information is available about them. Typically, more information is required to determine if the variant is disease related.
- Such information may include more extensive population data, functional studies, and tracing the variant in other family members who have or do not have the same health condition. **Parental testing can be useful to further delineate the variant classification.**
    - 1. Heterozygous: If the variant is found to be inherited from a parent, it would be supportive of benign status. If it is found to be de novo, it could be supportive of pathogenicity in the context of overlapping clinical features.
    - 2. Compound heterozygous: If the variants are found to be in cis/ on same allele, that would be supportive of benign status. If they are found to be in trans/ on different alleles, that could be supportive of pathogenicity in the context of overlapping clinical features.
- In some cases, we can measure an enzyme or transporter activity to evaluate the impact of the genetic variant on the protein, which is called a functional study.

Slide 21: Note that there is additional information in the full report from the company, including gene list, technical limitations of the test, coverage of genes (del/dup testing for each gene)

Slide 21:

- Team A: *What is the name of the genetic testing sent? What technology does it use? (Hint: read report)*
    - Answer: Multi-gene panel looking at periodic fever genes (one of which can cause lacunar stroke). It uses sequence analysis and deletion/duplication for 12 genes.
- Team B: *What disorder (s) does the gene cause? What is the clinical phenotype? (Hint: report, OMIM)*
    - Answer: DADA2, also known as Vasculitis, Autoinflammation, Immunodeficiency and Hematologic Defects Syndrome (VAIHS, OMIM 615688) is a monogenic systemic vasculopathy. Typical clinical manifestations of DADA2 deficiency include fever, elevated inflammatory markers, livedoid rash, and stroke, though there is wide phenotypic variation.



- Team C: *Is there any further biochemical testing that can be done to confirm the pathogenicity of the variant?*
    - Answer: Plasma activity of adenosine deaminase 2.
- Team D: *How is the variant classified?*
    - Answer: VUS. Help trainees read through the report and look up this variant on ClinVar. Tell them VUS can always be re-classified as pathogenic if there is phenotypic match and enzyme activity comes back as deficient.

Slide 23: Discuss that this patient's ADA2 activity resulted as nil or zero, **confirming her diagnosis of ADA2 deficiency**. It is unclear if the vertebral artery compression played a role in her initial ischemic infarcts. It is conceivable that this finding distracted from the diagnosis of DADA2 deficiency but given the location of his strokes, it is impossible to rule it out as a potential etiology of her initial strokes. **The diagnosis of DADA2 deficiency** was eventually made after she had another lacunar infarct in the setting of fever and systemic inflammation following her presumptively corrective spinal fusion.

Slide 24-25: Text from slide to discuss concepts of functional study. Enumerate some examples from neurological and non-neurological disorders.

Slide 26-28: Brief review of DADA2. Text from slide. **Emphasize that it is a treatable disorder, and we can prevent strokes.**

Slide 29: Take home points.

Slide 30: Suggested reading.

Slide 31: Acknowledgments.