FUTURE OF PEDIATRICS TALKS!

A VIRTUAL SUMMER SERIES

Pediatric Health Network

Children's National

A few notes about today's Webinar

- All lines are muted throughout the webinar.
- Please use the Chat function to ask questions or make comments.
- To avoid feedback noise, please do not have computer audio and phone audio active at the same time.
- Today's Webinar recording and slides will be posted to the PHN website following the presentation. www.pediatrichealthnetwork.org

Meet Our Speaker

Today's presenters have no conflicts to disclose:

- No financial or business interest, arrangement or affiliation that could be perceived as a real or apparent conflict of interest in the subject (content) of their presentation.
- No unapproved or investigational use of any drugs, commercial products or devices

Christina Grant, MD, PhD

Newborn Screening for Lysosomal Storage Diseases

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FUTURE OF PEDIATRICS

Goals/Objectives

- Overview Lysosomal storage disorders, red flags for referral and what requires emergent treatment
- Provide guidance for babies with positive screens
- Define pseudodeficiency
- Discuss how Genetics and Primary Providers work together to help families and keep babies safe in a pandemic
- Share resources for families while waiting for results

Lysosomal Storage Diseases on Newborn Screen

- Pompe Disease (GAA)
- MPS1/Hurler Syndrome (IDUA)
- Fabry Disease (GLA) (Maryland only)

- Pompe and MPS1- once symptomatic, damage is irreversible

- New disorders on screens- DC and VA since 2018, MD since 2019
  - **Cutoffs still being adjusted**
  - **6mo period (6/2019-12/2019)- ~125 babies referred, equals about 250 babies/year**

Pompe Disease (GAA)

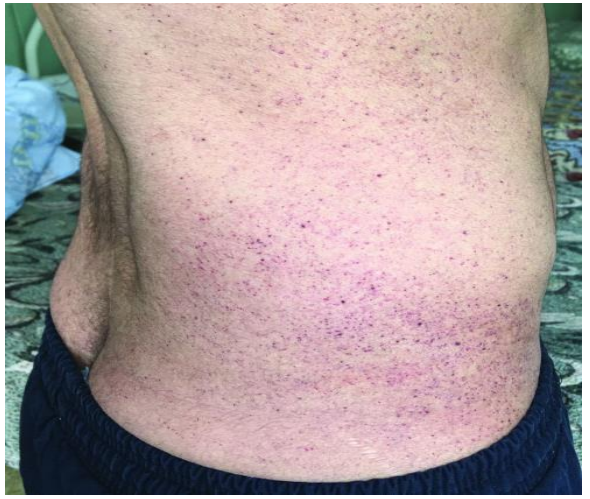
- Storage disease affecting primarily muscle (skeletal and cardiac)
- Infantile Onset- hypotonia/weakness, cardiomyopathy, poor feeding
- Late Onset- onset any time after fetal life (later infancy to late adulthood), weakness, usually no cardiac involvement
- Treatment- enzyme replacement therapy (time sensitive outcomes)
- High pseudodeficiency in certain Asian populations
- Infantile Onset Pompe is a true urgent
  LSD NBS condition
  urgent labs and ECHO, initiation of therapy

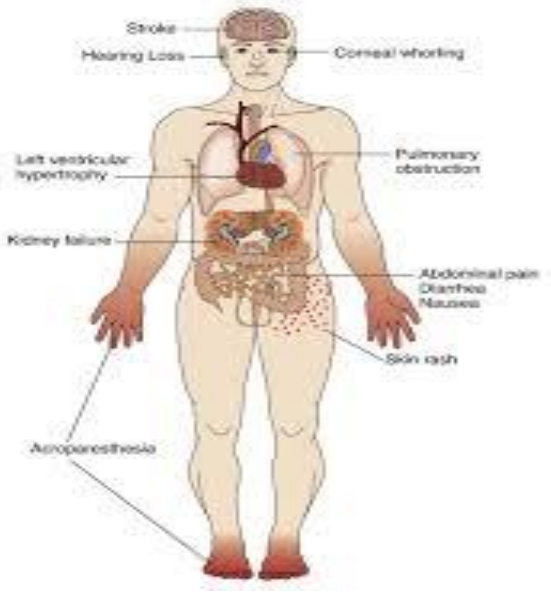
MPS I (IDUA)

- Storage disease affecting almost all organs, especially brain, skeleton, soft tissues
- Coarse features, developmental delay, macrocephaly, gibbous, hernias
- Very high pseudodeficiency in persons of African descent
- Treatment
  - HSCT/Bone Marrow transplant- preserves but doesn't 'fix' neurodevelopment (time sensitive)
  - Enzyme Replacement- helps soft tissue, does not affect neuro symptoms

Fabry Disease (GLA)- MD only

- Storage disease affecting nervous system, heart and kidneys starting in 2nd decade of life
- X-Linked, females can be symptomatic
- Classic form- renal failure, neuropathy, cardiomyopathy
- No treatment until late childhood (not an emergency), but often find affected family members
- Treatment- Enzyme replacement therapy, oral medication in some cases





Possible Results

- Positive- Critical/Lower than Expected
  - True positive
  - Pseudodeficiency (common): Genetic variation not associated with disease- enzyme is functional in the body but low activity on synthetic substrate or in lab conditions, common in certain populations (false positive)
  - Carrier
  - False Positive (repeat diagnostic enzyme is normal)
- Borderline (MD only)
- Inconclusive/Unsatisfactory
  - Controls not passed- does not mean positive
  - Usually requires repeat specimen

State Differences

Virginia and DC

- Usually Single Screen
- Enzyme 1st tier
- If abnormal, repeat enzyme level
- Genetic testing 2nd tier

VA: If critical, Genetics notified on enzyme, otherwise after genetic testing is complete, positive cases referred to genetics and PCP

DC: PCP notified if critical or with abnormal genetic testing (Genetics NOT notified in DC)

Maryland

- Two screens (or more)
- Enzyme only
- No additional/ 2nd tier testing done by state
- Positive on either screen often triggers referral
- PCP and genetics notified of result

What happens with a positive screen?

Pre-COVID

Positive NBS referred to genetics, most seen in person if appropriate

History and physical exam, counseling

Diagnostic testing (blood and urine), genetic testing for MD state screens

Results returned to family, letter to PCP and state follow-up by Children's National

Pros: see genetics quickly, faster TAT for some tests, genetics involved from start, counseling to family

Cons: in person visit, taking baby out of home, long drive in the city, PCP less involved in care

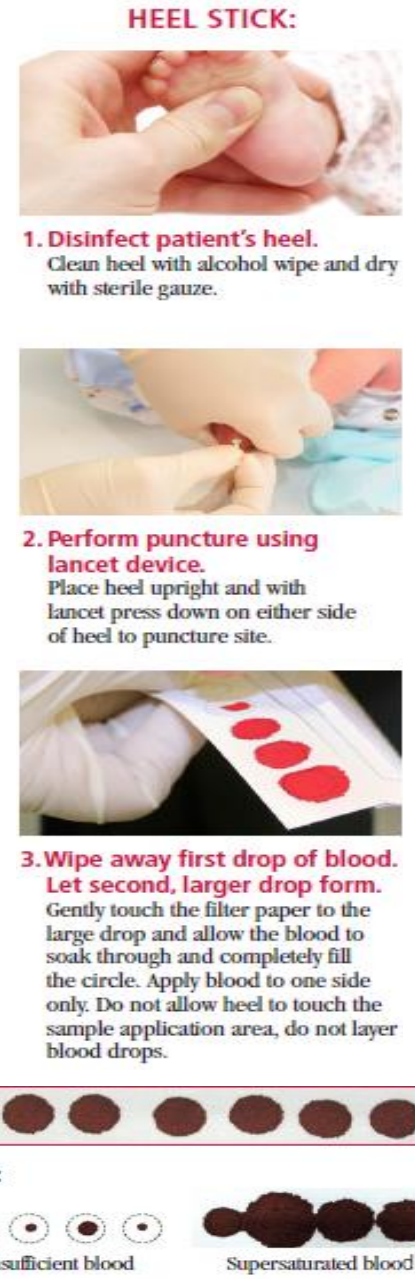
What happens with a positive screen?

How to keep babies safe during a pandemic

- Increased telemedicine use, increased PCP participation
- DC and VA screens- telemedicine visit to discuss results, counsel, and recommend a labs-only visit for diagnostic labs if indicated
- MD screens- Genetics reviews result, works with PCP office to arrange 2nd tier blood spot testing for genetic testing for appropriate patients vs labs only visit, followed by telemedicine once results back
- Urgent in person visit for any baby with concerning physical findings or genetic test results (discussion with genetics)

MD Screens- 2nd tier testing

- Genetics will work with PCP to determine best way to do secondary testing
- "Lantern Project"- sponsored project offering testing for babies with positive NBS or symptoms, easy to collect DBS in office and send
- Ordered by and results to genetics
  - Pros- free, keeps baby out of hospital, PCP maintains relationship and more involved
  - Cons- 3 week + TAT, parental anxiety, counseling after test, may still need to come in for follow-up testing



Case Example:

- Baby born in VA- Initial IDUA Enzyme levels low but not critical x2
- 2nd Tier genetics result available 5.5 weeks old:
  - 1 Pathogenic, 1 Uncertain genetic change
- Telemedicine at ~6 weeks with lab testing at Children's National the next day:
  - Biomarkers in blood and urine (GAGs): normal
  - Repeat enzyme level in leukocytes (diagnostic): low, without signs of storage
- Able to reassure family 1 week after labs that this was not severe disease, no need for bone marrow transplant

If enzyme had been critical, would have offered additional evaluation

Take Home- what do I do with a positive screen?

- Talk with genetics before referring patients!
- Red Flags- hypotonia, weakness, poor feeding, signs of heart failure in a baby with positive GAA/Pompe screen
- Fabry/GLA- never urgent
- Many false positives (especially in MD)- not every screen positive baby needs a formal genetics evaluation, but cannot become complacent- intervention sometimes time sensitive (weeks, not months)
- DC and VA screens- will often offer a telemedicine counseling visit, may recommend labs or in person visit
- MD Screen- will often recommend and help coordinate initial testing through PCP office given high false positive rate, then telemedicine or in person visit if needed based on results

Who do I call for help?

Generally, VA and MD will call you first, then us and we will reach out (DC only calls PCP)

Newborn Screen NP (near future) or NBS pager

- Call Children's National Hospital and ask for "Newborn Screen Pager" or "Newborn Screen Nurse"
- If you leave a VM with your info and baby's info, call will be returned!

Lysosomal Storage Team

- Christina Grant, MD, PhD
- Tamanna Roshan-Lal, MB ChB
- Debra Regier, MD, PhD (backup)

Resources for Families

Baby's First Test: https://www.babysfirsttest.org/

BearGenes Videos: https://childrensnational.org/departments/rare-disease-institute/beargenes

- Newborn Screening
- Pseudodeficiency
- Before your genetics visit: What to expect
- Also available as a free App in the AppleStore and GooglePlay store

Questions/Discussion

What happens with a positive screen?

Pre-COVID/Perfect world

- DC and VA screens referred by NBS program seen in person; MD screens discussed with PCP and many seen in person for follow up testing
- Full history, family history, and physical exam
- Follow-up testing including diagnostic enzyme and biomarker testing (blood and urine) and genetic testing for MD screens
- Counselling family about positive screen, possible results, and follow-up plan