Genetics and Inborn Errors of Metabolism

Cases Studies

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Case 1

- 5 day old with poor feeding
  - Exclusively breastfeeding
  - Decreased urine output
  - 10% below birth weight
- Prenatal history unremarkable
- Mother was GBS positive
- Delivered at 36 weeks via C section due to preterm labor
- Family History: parents are first cousins
Physical Examination
Physical Examination

- Temperature 39°, HR 155, RR 60, BP 60/25
- Lethargic
- Jaundice
- Liver extends 10 cm below costal margin
- Bilateral cataracts

• Differential Diagnosis?
Labs

- WBC 20,000
- AST 375, ALT 290
- Total bilirubin 17 mg/dL, conjugated bilirubin 7 mg/dL
- Prothrombin time 24, INR 2.6, PTT 47
- TORCH work-up negative
- Blood culture: *E. coli*
- Urine and CSF culture negative
- Abdominal ultrasound: hepatomegaly, ascites
Case 1

• Patient is treated with antibiotics for *E. coli* sepsis

• Once stable, enteral feeds are started with breast milk. His jaundice worsens and he develops bloody stools.
  – Necrotizing enterocolitis?
  – Milk protein allergy?
  – Intussusception?
  – Coagulopathy?
Galactosemia

Galactose pathway

Galactose → Galactose

Galactose - 1 - Phosphate

UDP-Gal-4-epimerase (3)

UDP-Glucose

UDP-Gal-1-P uridyl transferase (1)

UDP

Galactose

Glucose - 1 - Phosphate

GLUTZ
Classic Galactosemia

- Onset first days-weeks of life
- Jaundice (74%)
- Vomiting (47%)
- HSM (43%)
- FTT (29%)
- Lethargy (16%)
- Sepsis, especially *E. coli* (10%)
- Other: bleeding, cataracts, hypotonia, seizures
Galactosemia: Diagnosis

- Diagnosis usually made by NBS
  - GALT enzyme activity
- RBC Gal-1-P level
- Molecular testing (*GALT*)
  - Classic (0% enzyme activity)
    - Homozygous Q188R
    - Duarte (25% enzyme activity)
      - Q188R/N314D
- Bedside screen: positive urine reducing substances in the absence of glucosuria, along with clinical presentation
Galactosemia: Management

- **No breastfeeding;** use soy-based formulas
- Avoid milk & dairy products (lactose $\rightarrow$ glucose + galactose)
  - Calcium and vitamin D supplementation
- Monitor compliance by checking RBC galactose-1-phosphate
- Ophthalmology exam
Autosomal Recessive Inheritance

• Consanguinity
  – Marriages within a family
  – Small villages

• Isolated populations
  – Amish
  – Finland

• Bottleneck effect
  – Founder population
  – Extreme reduction in population size
Case 2

• 18 month male presents for well-child visit
• Weight at 25\textsuperscript{th} centile; height at 10\textsuperscript{th} centile; head circumference at 75\textsuperscript{th} centile
• Parents reports that he started walking independently at 16 months
• He currently says one word, good receptive language skills
Case 2
NF-1 Diagnostic Criteria

- ≥6 café au lait macules >5 mm in prepubertal individuals
- ≥ 2 neurofibromas of any type or 1 plexiform neurofibroma
- Inguinal or axillary freckling
- Optic glioma
- Lisch nodules (iris hamartomas)
- Distinctive osseus lesion (sphenoid dysplasia, tibial pseudarthrosis)
- 1st degree relative with NF
Autosomal Dominant Inheritance

- ✔ Variable expressivity
- ✔ Penetrance

- CAL
  - Tibial dysplasia
  - Neurofibromas

- CAL
  - Axillary and inguinal freckles

- CAL
  - Plexiform NF
  - Optic glioma

- CAL
  - Neurofibromas
  - Axillary and inguinal freckles

- CAL
  - Optic glioma
Case 3

• 8 year old male born to consanguineous Cambodian parents who are first cousins once removed
• Family history negative
• Developmentally delayed
  – First walked at 3 years of age
  – At 8 years he only speaks in short phrases and single words
  – Poor receptive language
  – Autistic-like behaviors
Physical Examination

- Long palpebral fissures, mild eversion of the lower lids
- Ptosis
- High-arched palate
- Low-set and posteriorly rotated ears
- Single transverse palmar creases with persistent fetal finger pads
- Fifth finger clinodactyly
- Short fifth toes with an increased gap between the first and second toes

Adam MP et al., *J Pediatr* 154:143-146, 2009
Case 3

• A diagnosis of Kabuki syndrome was entertained

• Diagnostic testing
  – Normal 46,XY karyotype at 550 bands
  – Normal FISH for 22q11 deletion and 15q13 duplication
  – Normal metabolic workup

• What would you order next?
Trisomy 18 Karyotype - 47,XY,+18

Chromosomes artificially straightened for illustrative purposes causing some apparent discrepancies in banding patterns of chromosome pairs.
Chromosomal Microarray
Case 3

Oligonucleotide array CGH demonstrated a *de novo* 1.1 Mb deletion of 19p13.3 that includes 30 known genes
STK11 is associated with autosomal dominant Peutz-Jeghers syndrome (PJS)
Peutz-Jeghers Syndrome (PJS)

• Gastrointestinal hamartomatous polyps, mucocutaneous pigmentation, increased risk of malignancy
  – Colorectal, small bowel, stomach, breast, ovarian, uterine, cervical, testicular, and pancreatic cancers

• Our patient had no mucocutaneous findings

PJS Tumor Screening

- Upper and lower endoscopy at age 8 years and every 2 years thereafter
- Annual testicular evaluations, including testicular ultrasound starting at age 10 years
- Colonoscopy beginning at age 25 years and every 2 years thereafter
- Endoscopic or abdominal ultrasound every 1-2 years from age 30 to evaluate for pancreatic malignancy

Case 4

- Newborn male with multiple limb defects
- Born at term to a 24 year old G2P1 mother
Case 4
Case 4

• What questions do you want to ask mother?
• What further studies would you like to order?
Case 4

- Diagnosis: Diabetic embryopathy
- Skeletal films: Tibial hemimelia bilaterally with femoral hypoplasia; normal upper extremities, no vertebral anomalies; normal sacrum
- Echocardiogram normal
- Renal ultrasound normal
- Chromosomal microarray: Normal male