Genetics in Pediatrics

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Why genetics matters:
- Major component and/or reason for pediatric admissions
- #1 cause of death in first year of life
- ~71% of children in hospital have a genetic disease or susceptibility
- ~3% of newborns with significant birth defect
- Families have concerns about recurrence, cause and available therapies

Practical genetic concerns
- Categories of genetic disease: chromosomal, single gene, multifactorial
- More specific tests available each year
  FISH probes for syndromes eg CHARGE, Williams, Cornelia de Lange
- For developmental delay, autism, microcephaly with/without major birth defects or facial dysmorphism, form a differential diagnosis and refer to Genetics
- Risk management: avoid missed/delayed diagnoses

Answer patient questions
- www has made info about genetic disorders available to public, parents may come to you with questions/concerns
- Children who do not speak by age 2 are delayed. Rule out hearing loss and/or autism/MR/specific speech disorder.
- Large part of outpatient visits are common disorders influenced by genetic background: asthma, obesity, ADHD

Points to remember
- The CDC recommends that all women of reproductive age take 0.4 mg folate daily to decrease risk of neural tube defects.
- Minimum time frame is one month before conception through first trimester
- A woman with a previous pregnancy with spina bifida, anencephaly, or encephalocele should take 4 mg folate 1 month before conception until delivery
- Certain drugs increase risk of NTD’s eg valproate. Is 4mg dose indicated?
- NBS will expand to include 23 more disorders. PCP’s need to know how to approach these.

Child 1
- On an 18 week ultrasound parents learned that their son had mildly shorter femurs, a ventricular septal defect, and a minimal nuchal fat pad. The mother had a low maternal serum AFP. The family elected serial ultrasounds for follow-up. What test are you likely to do at birth?
Chromosomes
- >2/3 of pregnancies with Down syndrome will have some combination of low MSAFP and ultrasound markers
- Amniocentesis, chorionic villus sampling, and umbilical blood sampling (not done routinely) can provide samples for prenatal diagnosis with regular banding or rapid FISH (fluorescent in situ hybridization)
- ~95% of children with Down syndrome have trisomy 21; others have translocation and/or mosaicism

Down syndrome - epidemiology
- Occurs in ~1/1000 births with increasing chance as mother’s age advances.
- Continuing efforts to make available: 1st trimester dx with nuchal fat pad measurements and biochemical testing; 2nd trimester dx with triple/tetra serum screening and ultrasound markers
- Age 35 and up, offer amniocentesis or CVS

Down syndrome - medical issues
- ~1/2 with congenital heart defect, AV canal
- Up to ~10% with hypothyroidism, celiac disease
- Up to ~7% with anatomic gut disease, e.g. duodenal atresia
- Up to 1% chance of leukemia
- Potential for atlanto-axial instability
- Microcephaly, short stature, frequent OM, tend to become overweight, cataracts, strabismus

Down syndrome – developmental issues
- Refer for early intervention assessment and services
- Continue with special education/inclusion
- Mild to moderate MR is usual
- Speech/communication therapy focusing on useful signs, articulation
- Physical and occupational therapies focusing on coordination, healthy weight and activity, and activities of daily living

Down syndrome – genetic counseling issues
- Part of prenatal assessment
- When breaking news, focus on:
  - the baby and positive aspects
  - one day at a time, esp. if sick
  - circle of support – other families, organizations, health care and education team
Child 2

- A couple from Turkey bring in their 2-month old with a concern about his overall sleepiness and floppy head. He is bottle fed. You look over his newborn discharge information and note good Apgars and initial feeding. What lab report do you want to see?

Newborn screen

- In Virginia, hemoglobinopathies, hypothyroidism, congenital adrenal hyperplasia, PKU, maple syrup urine disease, homocystinuria, galactosemia, biotinidase are screened at birth
- HOWEVER, pediatrician needs to verify results were done correctly or make sure it gets done
- MCAD was added in March 2004. Fatty acid oxidation disorder causing hypoglycemia. Easily treated with frequent feedings, avoid fasting
- 23 additional disorders to be screened in 2005

Newborn hearing screening

- Begun statewide in Virginia in July 2001
- Pass or fail with otoacoustic emission or automated ABRs as screen
- ~1 in 1000 babies with severe hearing loss
- >1/2 of congenital hearing loss is genetic with majority autosomal recessive
- Connexin 26 mutations responsible for majority of this

Hearing Loss

- NB screening will not detect mild hearing deficits or later onset of HL
- If speech is delayed or articulation is poor, test hearing even if NB screen was normal
- Congenital CMV is common cause of HL. May not develop until mid-childhood.

PKU - epidemiology

- ~1 in 15,000 births in US
- Currently screening in all 50 states, but need to insure no misses
- May not manifest in 1st 24 hours before protein feeding; antibiotics can lead to false negative screen
- Special formula without PHE is mainstay of treatment; start it as soon as possible
Phenylketonuria – medical issues

- Treatment reduces findings!
- Usually blonder than siblings with blue eyes, musty odor, MR
- Seborrheic eczematous skin lesions
- Restrict phenylalanine in diet so Phe levels stay close to normal range of 120-240 mmols/L. Do not over restrict; lifelong nutritional management is required.
- Avoid aspartame

PKU – developmental issues

- When untreated, abnormal EEG and ~1/3 with seizures
- Hypertonicity
- Hyperactivity with schizoid unsocial behaviors
- Treated, may still have perceptual motor and some learning problems
- Compliance is a problem, esp. in teens

PKU – genetic counseling issues

- Absent phenylalanine hydroxylase that converts Phe to tyrosine, a few are due to biopterin cofactor deficiencies
- Autosomal recessive with prenatal dx. Possible
- Transient hyperphenylalanemia occurs, esp. in premies
- Maternal PKU results in children with microcephaly, MR, heart defects – continue Rx in adults, esp. in pregnancy

PKU - resources

- American Academy of Pediatrics, Newborn Screening Fact Sheets
- Division of Consolidated Laboratories, Virginia Dept. of Health, 786-5195
- Scriver et al, The Metabolic Basis of Inherited Disease, McGraw-Hill

Child 3

- A foster parent brings a 5 year old girl to see you because the school says she will need to repeat kindergarten. She appears to have a small head and overall low growth. Her birth mother died in a car accident when the girl was 3. What historical information would be particularly useful to you?
Pregnancy exposure history and growth records

- The timing of onset of low growth, especially in head circumference, is very useful in considering causes and possible testing.
- Heavy (>7 drinks/week and/or binge) drinking in pregnancy has about a 1/3 chance of resulting in newborn presentation of FAS with microcephaly.
- Other exposures (eg infections) or underlying chromosome conditions are often have newborn microcephaly.
- Metabolic and degenerative conditions, as well as Mendelian conditions like Angelman syndrome and Rett syndrome, later onset of microcephaly.

FAS - epidemiology

- Very variable data with difficulty in ascertainment, ~1 in 100-1000
- Interaction of difficulties of alcoholism Rx, limited treatment programs, unplanned pregnancies
- Fetal alcohol spectrum disorders were recently redefined by specific criteria. Fetal alcohol effects is a description, not a diagnosis.

FAS – medical and developmental issues

- Classical FAS – HC < wt < ht, all <5%
- Small palpebral fissures, small fingernails, smooth philtrum with thin upper lip
- Increased risk of cleft lip/palate, congenital heart disease, joint abnormalities
- Variable mental retardation; specific pattern of learning and behavioral disabilities
- Poor complex problem-solving, hyperactivity, poor judgment, deficient social skills

FAS – genetic counseling issues

- ~30% chance of FAS with heavy drinking in initial pregnancy, however ~70% in a subsequent pregnancy
- IF YOU DON’T DRINK, YOUR BABY WILL NOT HAVE FAS!
- Plan pregnancies, pay attention to warning labels, help your friends.

FAS - resources

- AAP Committee on Substance Abuse, FAS and FAE, Pediatrics
- Dorris M, The Broken Cord
- FAS Family Resource Institute (www.fetalalcoholsyndrome.org)
- NOFAS (nofas@erols.com and www.nofas.org)
- Streissguth & Kantor, The Challenge of FAS, 1997
Angelman syndrome and Rett syndrome

- Angelman syndrome – postnatal microcephaly, seizures, laughter, large mouth, ataxia due to imprinting defect on ch. 15 (majority with deletion seen with FISH)
- Rett syndrome – postnatal microcephaly, seizures, hand wringing due to X-linked gene changes in MECP2, a gene silencer.
- Mostly girls described with Rett’s; but males have been affected, usually earlier onset and more severe deficits in boys.
- Angelman and Rett have severe to profound MR with little to no speech.

Child 4

- A 12 yr old girl is referred to you from the screening sports physical because the NP thought she had a heart murmur and a pectus. The girl is very focused on playing basketball. Her father died while swimming, and her mother doesn’t know that side of the family very well. What do you do?

Detailed physical exam and referral to cardiology and ophthalmology

- Heart findings in Marfan syndrome – MVP, aortic dilatation & dissection
- Eye findings – dislocated lenses, high myopia
- Skeletal – pectus, scoliosis, arachnodactyly, arm span/ht >1.05, low US/LS, wrist and thumb signs
- Other - dural ectasia, pneumothorax, striae, incisional hernias

Marfan syndrome - epidemiology

- >100,000 in US with the condition
- Other related disorders can occur with other alterations in the microfibril of the connective tissue
- 75% will have affected family members; 25% are new mutations

Marfan syndrome – genetic counseling issues

- Clinical diagnosis with + family hx & 2 organ systems, or if – family hx, 3 organ systems
- Autosomal dominant condition with varied changes in fibrillin gene on ch. 15
- Linkage and mutation testing potentially available
- Pregnancy is higher risk
Marfan syndrome – resource issues

- National Marfan Foundation (www.marfan.org and 800-8-MARFAN)
- www.genereviews

Child 5

- An 18 yo boy’s mother is dying with breast cancer. He has always had problems in school but is graduating. He has been having significant thigh pain recently. He is afraid it is cancer and doesn’t want to see a doctor. Is it cancer?

Family history and physical exam are needed

- All cancer is genetic in that it represents unregulated growth.
- ~10% of cancers are highly familial.
- Most cancers represent the interaction of environmental effects with genetic changes, some of which may be inherited.
- Some genetic conditions have higher likelihoods of certain types of cancer.

Syndromes with increased cancer risk

- Beckwith-Weidemann, an overgrowth syndrome, Wilm’s and liver tumors
- WAGR: Wilm’s tumor, aniridia, growth retardation
- Bannayan-Riley-Ruvalcaba: Macrocephaly, pigmented lesions, thyroid, colon, CNS tumors
- Tuberous sclerosis: ashleaf spots, seizures, rhabdomyosarcomas

Cancer susceptibility syndromes, neurofibromatosis - epidemiology

- ~1/3 of persons in US develop cancer
- ~5-10% of breast cancer is highly familial with BRCA1-2 changes accounting for the majority of this.
- Many inherited cancer susceptibility genes represent tumor growth suppressors or DNA repair mechanisms.
- NF-1 occurs in ~1 in 3000 persons and has ~8% risk of cancer
Neurofibromatosis-1

Medical issues
- Physical exam for 6 or more CAL (>0.5 cm in <6 yo, >1.5 cm after, axillary/groin freckling, Lisch nodules, neurofibromas and other findings
- In newborn period, optic gliomas and pseudoarthroses
- In childhood, scoliosis and learning disabilities
- Lifelong – possible pain and cosmetic issues, hypertension, body asymmetry, ~8% malignant transformation
- NF-2 - vestibular schwannomas

NF-1 genetic counseling issues
- Autosomal dominant with variable severity
- May see increased neurofibromas with hormonal changes of puberty and pregnancy
- Very large gene on ch. 17, normal NF-1 product regulates normal cell proliferation, protein truncation test variably useful

NF-1 resources
- National Neurofibromatosis Fdn (1-800-323-7938 and www.nf.org)
- Neurofibromatosis Institute, 5415 Briggs Ave., La Crescenta, CA 91214
- Goldberg Y et al, “NF Type 1”, Clinical Pediatrics, p. 545, Nov. 1996

General pointers
- Do an excellent physical exam; skin markers, body build, distinctive faces
- Do a relevant family history
- Consider obtaining chromosomes when there are 3 or more anomalies, including growth issues and neurosensory anomalies
- Make sure the bases are covered – newborn screen, growth plotted, miscarriages/stillbirths, & genetic history reviewed
- Trust your instincts and train them!

Practical pointers
- Get to know your local geneticist for consultation and referral
- Geneticist and genetic counselor listings are available through the American Board of Medical Genetics and the National Society of Genetic Counseling
Resources

- Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim)
- GeneClinics (formerly, now www.genereviews.org)
- Smith’s Recognizable Patterns of Human Malformation
- The Genetic Alliance (formerly Alliance of Genetic Support Groups) www.geneticalliance.org