Genetic Red Flags in Well-Checks

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Faculty

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  – Serves on the University Hospital Bioethics Committee
  – Co-Director of The Neurofibromatosis Center of New Jersey
  – A Founding Fellow of the American College of Medical Genetics and Genomics
Disclosures

Dr. Pletcher has no financial relationships or conflicts of interest to disclose relevant to this presentation.
Learning Objectives

• At the end of this presentation participants should be able to:
  – Identify reasons for referral to a geneticist
  – Express the value of a genetic evaluation
  – Employ strategies for approaching parents about a potential genetic referral
Neonatal Referrals

Finding

• Abnormal newborn screening test
• Congenital hypotonia or hypertonia
• Unexplained intrauterine growth retardation (IUGR)

Why to Consider

• R/O inborn error of metabolism
• R/O chromosomal, metabolic or syndromic dx
• R/O chromosomal, metabolic or syndromic dx
# Neonate, Infant or Child (1)

## Finding
- Single major or multiple minor anomalies
- Dysmorphic features that are not familial +/- dev delays
- Known metabolic condition or symptoms of a metabolic disorder
- Abnormal brain MRI findings - malformation, leukodystrophy, periventricular calcifications

## Why to Consider
- R/O chromosomal or syndromic diagnosis + recurrence risks
- R/O chromosomal or syndromic diagnosis
- Diagnose the disorder, initiate treatment and management + recurrence risks
- R/O chromosomal or syndromic diagnosis
Neonate, Infant or Child (2)

**Finding**
- Unusual growth pattern – overgrowth, short stature, hemihyperplasia
- Possible connective tissue disorder – joint laxity, poor healing, marfanoid habitus
- Congenital eye defect
- Significant deafness or hearing loss not secondary to recurrent otitis medias

**Why to Consider**
- R/O chromosomal or syndromic dx – BWS, Turner syndrome, Sotos syndrome
- R/O Ehlers-Danlos, Marfan syndrome etc...
- R/O syndromic diagnosis
- R/O syndromic or non-syndromic form of hearing loss
<table>
<thead>
<tr>
<th>Finding</th>
<th>Why to Consider</th>
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<tbody>
<tr>
<td>• Cardiomyopathy not secondary to viral infection</td>
<td>• R/O mitochondrial or metabolic condition</td>
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<tr>
<td>• Six or more café-au-lait spots greater than 0.5 cm</td>
<td>• R/O neurofibromatosis (NF) type 1</td>
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<tr>
<td>• Unusual skin findings or multiple types of lesions</td>
<td>• R/O chromosomal or syndromic diagnosis</td>
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<td>• A parent with a known chromosomal abnormality or rearrangement (especially if dysmorphic or delayed)</td>
<td>• R/O chromosomal abnormality</td>
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Neonate, Infant or Child (4)

Finding

• Bilateral or multifocal malignancies (Wilms or retinoblastoma)
• Clotting disorder such as hemophilia or thrombosis
• Suspected chromosomal or syndromic diagnosis
• Significant family history of medical or psychiatric problem that may affect your patient

Why to Consider

• R/O cancer syndrome or other chromosomal or syndromic diagnosis
• R/O inherited clotting disorder
• Dx confirmation, prognosis, management + recur risk
• Counseling for diagnosis, diagnostic testing, inheritance and risk assessment
Child Referrals

Finding

- Unexplained intellectual disabilities or dev delays
- Autism or pervasive developmental disorder
- Unusual behaviors, esp when seen with dev delays
- Progressive muscle weakness
- Other neurologic condition with genetic implications

Why to Consider

- R/O chromosomal, syndromic or metabolic dx
- R/O chromosomal or syndromic diagnosis
- R/O chromosomal or syndromic diagnosis
- Confirm suspected muscle or nerve diagnosis
- R/O genetic diagnosis
List of Reasons for Referral

• Neurologic Issues
  – Significant intellectual disabilities or developmental delays
  – Autism spectrum disorder
  – Hypertonia, hypotonia or spasticity
  – Hard to control seizures
  – Brain malformation
  – Congenital deafness

• Congenital Anomalies
  – Heart defect
  – Diaphragmatic hernia
  – Renal agenesis
  – TE fistula
  – Limb or bone malformation
  – Dyshomorphic features

• Growth Problems
  – Intrauterine growth retardation
  – Small for gestational age
  – Failure to thrive
  – Short stature
  – Disproportionate growth, overgrowth, hemihyperplasia or marfanoid habitus
  – Microcephaly or macrocephaly

• Miscellaneous
  – Abnormal skin findings – café-au-lait spots, multiple lipomas, ash-leaf spots
  – Cardiomyopathy without viral cause
  – Clotting abnormalities – thrombosis or excessive bleeding
  – Multifocal or bilateral malignancies such as Wilms tumor or retinoblastoma
Benefits of a Genetic Referral

• Having a confirmed genetic diagnosis can:
  – Highlight potential complications
  – Guide diagnostic studies or surveillance strategies
  – Provide important prognostic information
  – Guide EIP or IEP services and assist the Child Study Team
Case #1
Cytogenetic Diagnosis and Surveillance

• Newborn male referred because of a ventricular septal defect (chromosomes normal)

• At surgery thymic hypoplasia was noted, genetics was consulted, and FISH testing for a 22q deletion was performed

• This test was positive and dad was evaluated and found to also carry this deletion
Case #1
Follow-Up and Surveillance

- Child evaluated for hypocalcemia (this was identified) and he was placed on a synthetic vitamin D analog to increase calcium levels
- He was enrolled in an early intervention program and received services prior to enrollment in a preschool handicapped program
- He was evaluated for T-cell deficiency and provided prophylactic antibiotics
Case #2
Cytogenetic Diagnosis and Surveillance

• Infant referred for dysmorphic facial features
• Chromosome analysis was performed and demonstrated extra-genetic material on chromosome 22
• Child was referred for renal sonogram and echocardiogram despite no cardiac murmur
• He was eventually found to have a single kidney and total anomalous pulmonary venous return that required immediate surgery
Case #3
Cytogenetic Diagnosis and Surveillance

• 5 ½ year old girl referred for speech delays and streaky hyperpigmentation of the skin
• Child is in a regular kindergarten class and receiving speech therapy twice a week
• Teacher feels she is not trying very hard and needs to be more motivated with handwriting
• Chromosome analysis demonstrates a mosaic marker chromosome (isodic 9p) = two extra copies of 9p
Case #3  
Conclusions

- This chromosomal change is likely associated with more significant learning issues (noted hypotonia and weak hands)
- Echocardiogram and renal ultrasound are recommended
- School placement should be re-evaluated and service provision increased to include OT/PT
- Risks for recurrence are very small for parents
Case #4
Neurofibromatosis Type 1

• A 2 ½ year old boy is referred for 6 café-au-lait spots, but no other features of NF
• Neurodevelopmental assessment is normal
• He is also referred for a dilated eye exam by a pediatric ophthalmologist
• Exam is significant for pallor of the left optic nerve
• Subsequent MRI demonstrates a left optic nerve glioma
Case #4
Follow-Up

• Close follow-up of the vision in the left eye over 6 months shows decreasing visual acuity

• He is referred for chemotherapy for the optic nerve glioma (ONG) and has a wonderful response to treatment with shrinkage of the ONG and return of vision on the left

• He is followed yearly by the multidisciplinary NF team and monitored for complications of NF1
Case #5
Disaster Avoidance

• 12 year old boy from Puerto Rico with albinism is referred for genetic evaluation and counseling because his mom is pregnant

• He has typical features of albinism with nystagmus and poor visual acuity, blonde/red hair and fair skin with some freckles

• He is asked about easy bruising and his mom and he report that he does in fact bruise quite easily
Case #5

Conclusion

• Based on this “tip” we suspect that he has Hermansky-Pudlak syndrome instead of simple albinism (even though both are autosomal recessive conditions)
• He is at risk for excessive bleeding with minor and major surgical procedures, pulmonary fibrosis and granulomatous colitis
• Knowing this we can better prepare for surgeries in the future (DDAVP and hematology evaluation), no aspirin, close pulmonary follow-up (no smoking!) and monitor for GI symptoms
Case #6
The Medical Odyssey

• A 4 year old child with autism has been evaluated and followed by his pediatrician and developmental pediatrician since his diagnosis at the age of 2 years
• He has been seen by a dermatologist for vitiligo, a neurologist for hypotonia, and a nephrologist for a kidney cyst detected incidentally on a scan after a urinary tract infection
• Summertime exam demonstrates several well-demarcated hypopigmented macules and the diagnosis is...tuberous sclerosis
Case #7
Pregnant Family Member

• A woman is referred for genetic counseling because her sister is pregnant and she has two children with severe intellectual disabilities and minor birth defects

• The family history is otherwise unremarkable and prior genetic testing including chromosome analysis on the brother and sister were normal/negative

• A CGH microarray is ordered on the daughter for completeness’ sake
Case #7 Pedigree (A)

Purple = affected
Case #7 Pedigree (B)
Case #7 Conclusion

• Pregnant sister is actually at risk of being a translocation carrier and could also have an affected child

• Immediate specialized cytogenetic studies should be offered to her to assess her risks and determine if prenatal testing is indicated
Talking to Parents about a Genetic Referral

- Dealing with reticent or anxious parents
  - “On my exam today I see _X finding_. I want to be sure there isn’t a genetic connection and, in order to be thorough, I am recommending that we seek the advice of a geneticist.” BAP
  - “_Jonny/Joanie_ has been diagnosed with __(a learning disorder/autism/developmental delays)__ and I would like to see if we can identify a possible cause for these difficulties. Therefore I am suggesting that __Jonny/Joanie__ be seen by a geneticist.” BAP
  - “In order to address your question, I would like to refer to Medical Genetics.” JM (John Moeschler)
  - “In order to best care for your child, I would like Medical Genetics to help me with the following question: ___________________?” JM
  - “I understand you are not concerned, but in order to provide best care, I need __________ from Medical Genetics.” JM
Preparing Patients for the Genetic Visit

• Provide reports from imaging studies if possible
• Provide lab results (especially any prior genetic tests) as well as recent routine blood work – CBC, CMP, TFTs etc…
• Ask parents to bring copies of the school or program evaluations – PT, OT, ST and testing
• Provide reports from other subspecialists such as a developmental pediatrician, pediatric neurologist, gastroenterologist, endocrinologist, cardiologist, surgeon etc…
Parents May Want to Know

• What are the benefits of genetic testing and what are the risks?
• Can having a genetic diagnosis help us with educational planning?
• Can having a genetic diagnosis help us with family planning?
• Will having this information potentially impact other family members? If so, how do I go about telling others in the family?
Parents May Need to Know

• Gathering some general family history information prior to the genetic visit may make the family history taking easier (like ages or causes of death, major medical diagnosis such as birth defects, as well as physical and intellectual disabilities).
• For many children, genetic evaluation fails to provide a specific diagnosis, even with the high tech testing available now.
• Some children may benefit from a revisit with the genetic team in the future to see what new tests are around or if the features or clinical findings change over time.
Bibliography

Questions
Thank you for your participation!

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www.GeneticsinPrimaryCare.org
Please join us for our next webinar!

Genetic Testing in Primary Care
Faculty: Lee Zellmer, MS, CGC
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