Genetics Evaluation, Referrals, and More—What To Do Next

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Thursday, June 28
12:00 - 12:30pm Central

Time Out for Genetics Webinar Series
Presented by the Genetics in Primary Care Institute

Drs Greene and Moeschler have no financial relationships or conflicts of interest to disclose relevant to this presentation.
Acknowledgments

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Learning Objectives

1. Explain what families and patients can expect from a medical genetics consultation
2. Describe the role of primary care providers in medical genetics consultations including,
   a) When the medical home should consider requesting genetics consultation; and
   b) How the medical home can initiate and facilitate the evaluation process
3. Discuss the value of appropriate medical genetics consultations, care coordination and co-management and benefits for patients, families and the medical home
Presentation Overview

- What parents and patients want and need from a genetics consult
- What primary care providers can do to help the process work for patients and for them
- What Medical Geneticists can do for those with common (rare) pediatric problems
- How specialists—medical home—families might imagine working effectively

Presentation Overview

- Part 1 will focus on the office visit of an infant, child or adolescent who is not acutely ill; and
- Part 2 will further address issues relating to inborn errors of metabolism in the office, on the wards, or in the emergency room
- Wrap-up with summary and consider strategies for successful co-management in evaluation for genetic conditions
Medical Home—Medical Genetics Referrals

- Those who present in the Medical Home with problems of:
  - Growth
  - Development and/or abnormal neurologic exam
  - Structures (anomalies)

What Parents and Patients Want

- Health care that responds to the needs (wants) when they need (want) it, in the way they need (want) it, every time they need (want) it
- Responsive and efficient
- Family-centered and culturally competent
- Wise and empathic
- Reliable and safe
Expected Benefits from Medical Genetics

For child/patient | For families
---|---
Improved health outcomes | Understanding that comes from genetic counseling including family planning discussion
Improved health care and surveillance | Health care changes (for some)
Improved understanding of condition | Diagnostic testing for other family members, if warranted.
Improved educational planning | Understanding of condition
End unwarranted medical testing and treatments | Social support and peer networking

Expected Benefits from Medical Genetics

- *Etiological* diagnosis
- Treatment plan based on etiology, pathogenesis and/or phenotype
- Explicit “care-sharing plan” involving who does what when for what period of time, designed by all three parties
  - Ongoing evaluation if no diagnosis
  - Co management as appropriate regardless whether there is diagnosis
Medical Home

• Educate and “activate” patient
  – “In order to address your question, I would like to refer to Medical Genetics.”
  – “In order to care best for your child, I would like Medical Genetics to help me with the following question: ______________.”
  – I understand you are not concerned, but in order to provide best care, I need _____ from Medical Genetics.

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<thead>
<tr>
<th>TABLE 1</th>
<th>What Families Might Expect From the Clinical Genetics Evaluation</th>
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<tbody>
<tr>
<td>Before visit</td>
<td>Request for child's medical charts; neurodevelopmental test results; all medical test results; copies of MRI, CT, or other imaging studies; Request to bring photographs of child and family members; Asked about the family history; Asked to set aside sufficient time for prolonged consultation</td>
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<td>At the visit</td>
<td>Clarify the purpose of the visit; Review the child's medical history and neurodevelopmental status; Review family history (≥3 generations); Complete physical and neurologic examinations; Geneticsist's initial impressions discussed</td>
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<tr>
<td>After the visit</td>
<td>Clinical photographs; Laboratory studies (blood and/or urine tests); Arrangements for MRI or CT studies; Arrangements for other consultations (e.g., neurology, developmental pediatrics, ophthalmology, etc); Arrangements for ongoing communication and follow-up visits</td>
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Case Example

- 6-month infant girl referred for global developmental delays and epilepsy
- Has “retinal lacunae” and vision impairment
- Noted agenesis of the corpus callosum on brain MRI
- Thoracic vertebral anomalies
- Answer?

Aicardi Syndrome

- Presumed X-linked (dominant)
- Gene: unknown
- “Metabolic testing” no need
- Microarray no need
- Treatment: “symptomatic”
- www.genetests.org
- www.aicardisyndrome.org
Noteworthy Signs and Symptoms That Prompt a Referral

- Disorders of child development:
  - Global developmental delay
  - Intellectual disability
  - Autism spectrum disorders
  - Other neuro-developmental syndromes or symptoms of unknown cause (e.g., idiopathic infantile epileptic encephalopathies, multisystem disorders with regression, etc.)

Medical Genetics Evaluation: Developmental Delay, ID

1. Clinical History
2. Family History
3. Physical examination (especially for minor anomalies)
4. Neurological examination
5. Specific confirmatory genetic tests for suspected syndromes
6. Microarray CGH
7. Fragile X Molecular genetic testing
8. Metabolic screening in all
9. Targeted MRI brain imaging
Noteworthy Signs and Symptoms That Prompt a Referral

- Disorders of growth:
  - Short stature, disproportionate
  - Short stature, proportionate, when with developmental delays or anomaly (major or minor)
  - Somatic overgrowth

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<tr>
<th>Symptom or sign</th>
<th>Syndrome</th>
<th>Gene or karyotype</th>
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<tbody>
<tr>
<td>Developmental Delay</td>
<td>Fragile X syndrome, Klinefelter syndrome, McDermid-Phelan syndrome, 47,XXY &quot;syndrome&quot;, Mosaic trisomy 8, Sotos syndrome, PTEH hamartoma tumor syndrome</td>
<td>FMR1, XXY, 20p-3 deletion, 47,XXX, +8 mosaicism, NSD1</td>
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<tr>
<td>Dysmorphology</td>
<td>Beckwith-Wiedemann syndrome, Sotos syndrome, Simpson-Golabi-Behmel syndrome, Weaver syndrome, Perlman syndrome, Nevus syndrome (EHlers-Danlos syndrome, kyphoscoliotic type), Marshall-Smith syndrome</td>
<td>11p15 uniparental disomy, CDKN1C, H19</td>
</tr>
<tr>
<td>Disproportionate growth</td>
<td>Marfan syndrome, Klinefelter syndrome, Homocystinuria</td>
<td>FBN1, 47XXY, CRIS</td>
</tr>
<tr>
<td>Other syndromes to consider</td>
<td>San Filippo syndrome (Mucopolysaccharidosis, type IIIA, B, C, D), Sclerosteosis</td>
<td>Several genes, SOST</td>
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Noteworthy Signs and Symptoms That Prompt a Referral

• Disorders of structure:
  – Major anomalies (more than one or one in association with minor anomalies),
  – Minor anomalies, (single and multiple),
  – Infant or child with dysmorphic features, particularly if present with short stature and/or neuro-developmental disorders

Referral of patients with dysmorphic features

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<tr>
<th>Key considerations:</th>
<th>Refer if present:</th>
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<tr>
<td>Developmental delays</td>
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<td>Abnormal growth</td>
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<td>Organ dysfunction or chronic illness</td>
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<td>Multiple minor anomalies</td>
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<td>Concern that genetic syndrome might be present</td>
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Bring it together - what to DO?

- Term, BW 1.9 KG; “DD”
- Mother 27 y.o. G3 P3; left high school because of dyslexia
- 5 y.o. female sib S/P TEF repair; in developmental preschool for mild ID
- 3 y.o. male sib, healthy, also in developmental preschool

How Common are Inborn Errors of Metabolism (IEM)?

- “Individual” disease frequency varies 1/1000 to 1/10,000 to 1/1,000,000
  - PKU - 1/15,000, Galactosemia, NKH each - 1/50,000, Homocystinuria - 1/200,000
  - Mitochondrial disease 1/1000!!!
- Differing frequencies in different ethnic groups
  - Eg. Tay-Sachs disease – 1/4000 in Ashkenazi Jews and 1/400,000 in General population
- Collectively common: more than 1-2/1,000
  - There are a LOT of IEM – many undiagnosed
Genetic disorders – including IEM – are more common in those with severe or unusual health problems than in the healthy population.

Reasons to Consider IEM

- **Specific** therapy to improve outcome may be available:
  
  “With the potential availability of treatment, the rarity of individual disorders is no longer a valid reason for not considering them”

- *Restrict substrate
- *Replace missing product
- *Remove toxic metabolite
- *Cofactor Therapy ("Megavitamins")
- *Enzyme replacement
- Organ Transplant
- [Gene therapy]
- Anticipatory guidance - supportive therapy
Normal CBC?

- 4 year old boy with developmental disability
- WBC 8,460; unremarkable differential
- H/H 11.6/37
- Platelets 137K
- MCV 97

Inherited Metabolic Disorders: Clinical Presentation in the Newborn

- Asymptomatic
- Acute neurologic symptoms only
- “R/O Sepsis” (systemic, +/- GI and +/- neurologic symptoms) without acidosis
- “R/O Sepsis” with acidosis
- Dysmorphic +/- organomegaly, +/- “R/O Sepsis” and +/- acidosis
- Abnormal newborn screen (not addressed today)
Presentations of Metabolic Disease:
Acute or Chronic, Static or Progressive, Any Age

- With or without
  - abnormal growth
  - behavior or neurologic abnormalities
  - malformations
  - dysmorphic features
  - abnormal function of the brain, eyes, skin, hair, hearing, lungs, heart, muscles, bones, joints, intestines, bone marrow, endocrine system...
- As an isolated symptom or sign, or as a “syndrome”
- In a single individual or in family members
- With or without another diagnosis—eg, “migraine” or food allergy, or “viral syndrome”

Proof of Another Condition Does NOT Rule Out Possibility of IEM

- E. coli sepsis occurs with increased frequency in galactosemia
- Hepatitis – or RSV – can precipitate 1st episode of metabolic crisis in MCAD
- Organic acidemia or other IEM can cause increased irritability and result in increased risk of non-accidental trauma

What is the chance that a child with diabetes will have PKU? or CF?

What is the chance that a child with muscular dystrophy will have glycerol kinase deficiency?
Behaviors Caused By IEM

- Developmental disability
- Autistic-like behavior
- Mood changes – irritability, euphoria
- Energy level – irritability, fatigue
- Sleep disturbance – nightmares, night awakening, bed wetting
- Feeding – food refusals, food craving, vomiting
- Attention/concentration disorders
- Aggression – self-abuse, violent outbursts
- Impulsivity, poor judgment
- Psychosis

Focusing the Evaluation for Metabolic or Other Genetic Disease:

- History
  - Patient and family
- Physical Examination
  - Patient and family
- Laboratory or other testing
  - “Screening” (when appropriate) or specific (when appropriate)
History As a Clue to IEM

Example of angiokeratoma around belly button.
Reproduced courtesy of Dr Thomas Jansen.
Shire Human Genetics Therapies, Inc.

Examination – Clues to IEM
Put it Together: “Screen” for Genetic (including Metabolic) Disease

1. **History** – including family history
2. **PE** – include growth, dysmorphology, neuro exam
3. **Consider refer** to Genetics OR
4. **Basic Laboratory Studies**
   1. Dysmorphic with or without ID –
      1. Microarray (Karyotype)
      2. With ID/DD consider imaging brain
   2. Non-dysmorphic and “non-systemic”, with or without ID – also look for evidence of IEM
   3. With “systemic” signs and symptoms—also look for evidence of IEM

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**Laboratory Testing for IEM**

- **Enzyme A**
- A → B → C → F
- **cofactor**
- Test for:
  - Evidence of altered physiology
  - Evidence of increased or decreased levels of metabolites

- D → E
IEM “Screening” Studies

- CBC (include the MCV!)
- Electrolytes and LFTS
- CPK
- Blood amino acids
- Consider urine mucopolysaccharides;
- Consider urine organic acids, blood acylcarnitine profile, carnitine total and free

- Normal Electrolytes?
  - Na 142
  - K 4
  - Cl 102
  - Bicarbonate 22

Normal Urinalysis?

- pH 5.5
- SG 1.022
- Dipstick negative

- Sample from a toddler collected at admission for “D&V” with moderate dehydration after 1 ½ days of very poor intake (and mom is a good historian) with blood glucose 62
Child with Abnormal Neurologic Exam or Acute/Recur Illness

• “Screen” with:
  – CBC, electrolytes, liver enzymes, CPK
  – Blood amino acids, acylcarnitine profile, carnitine total and free
  – Urinalysis, urine organic acids, urine MPS
  – Ammonia when mental status is acutely altered
    – special considerations for collection and handling—typically possible ONLY in hospital
• “Special” studies if/as indicated

When to Pursue Special Testing for IEM or Other Genetic Conditions

• Based on history, PE, and any results of basic studies—next steps based on differential diagnosis
• Team decisions—MH, genetics and FAMILY
• Examples—
  – ID, cleft palate and syndactyly 2-3 toes—possible Smith Lemli Opitz
  – FTT + hypotonia—possible Prader Willi Syndrome; possible fatty acid oxidation or mitochondrial disease
  – Previously healthy and non-dysmorphic child with slowing development—possible PKU missed by newborn screen, possible lysosomal storage disease, possible mitochondrial disease
  – Recurrent admits for “D&V” (especially w/o diarrhea!)—possible urea cycle defect, organic acidemia or fatty acid oxidation defect
In Summary: Approach to IEM or Other Genetic Condition

- **Suspicion**
  - History (including family history) and physical examination

- **Diagnosis**
  - History, physical examination
  - Diagnostic studies (not just DNA! – various laboratory studies and imaging)

- Treatment and/or anticipatory guidance
- Education/Counseling

Team Approach for Child & Family

- To achieve goal of understanding the child and helping the child and family we should:
  - Understand value of diagnostic genetic testing – avoid under-testing or over-testing

- Use consultation and teamwork – options:
  - Begin testing before referral
  - Refer for evaluation before testing
  - Call to discuss options
Questions?

Thank you for your participation!

For more information, please contact
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nstevens@aap.org
847/434-4738

www.medicalhomeinfo.org/GPCI.aspx
Time Out for Genetics

Registration is now open for

“Myths of Primary Care Providers and Patients/Families Regarding Genetics—Setting the Record Straight”

Thursday, July 26
12:00 - 12:30pm Central

https://www2.gotomeeting.com/register/494408034