Recognizing Genetic Red Flags in Clinical Evaluations

Overview
DNA contributes to variation in health across the human lifespan. Conditions due to specific genetic changes can present at any age, and genetic susceptibilities can also contribute to how children respond to infection, trauma, and other environmental influences. Clinical findings gleaned from the medical history, the family history, and the physical exam (so-called red flags) may be particularly suggestive of possible genetic conditions or other genetic factors, and awareness of such red flags is part of incorporating genetic thinking into the medical home. Paying attention to red flags and minimizing missed opportunities for diagnosis, prevention, and treatment are vital duties of the primary care provider. The following case illustrates the importance of paying attention to red flags throughout a child’s life.

Learning Objectives
Upon completion of Recognizing Genetic Red Flags in Clinical Evaluations, residents should be able to

- identify specific clinical findings that suggest a possible genetic condition,
- recognize family history details that raise concern about a possible genetic condition,
- list reasons for referral to a geneticist or genetic counselor in a pediatric practice, and
- educate parents about available informational resources in genetics.

Case Presentation
Initial Presentation (Red Flag 1—Hypotonia)
You first meet Adam at his 2-week well-child visit. He is mildly hypotonic and at the 5th percentile in height and weight. Breastfeeding was established in the first several days after birth, and his mother has no concerns about his feeding.
**Question 1.** Which of the following features would, if present, be least likely to make you consider referring a patient to a geneticist for hypotonia in the first month of life?

(A) Gestation age of 32 weeks
(B) Distinctive facial appearance
(C) Abnormal newborn screen
(D) Seizures
(E) Microcephaly

Compared to full-term newborns, premature newborns often have lower tone that improves as they reach a chronological age of 40 weeks. Resolving hypotonia that is within the range of the normal variation makes a genetic cause somewhat less likely. Persistent or worsening hypotonia should be monitored more closely. Thus, a child who is persistently or increasingly hypotonic, especially when hypotonia impairs feeding, merits the following actions:

- Review of newborn screening results
- Detailed physical examination to look for major and minor anomalies
- Collection of detailed family and pregnancy history
- Careful measurement of growth parameters, including head circumference
- Evaluation for the presence of additional neurologic abnormalities, such as seizures

**Question 2.** Which of the following is least likely to cause transient neonatal hypotonia?

(A) Prader-Willi syndrome
(B) Congenital myopathy
(C) Spinal muscular atrophy
(D) In utero stroke
(E) Leukodystrophy (one of several white matter diseases, such as some lysosomal storage, mitochondrial, and peroxisomal conditions)

Hypotonia may be the presenting sign for many systemic diseases and diseases of the nervous system. The differential diagnosis for neonatal hypotonia includes the following conditions:

- Congenital myopathy
- Congenital muscular dystrophy
- Congenital myotonic dystrophy
- Congenital myasthenia gravis
- Familial dysautonomia, especially in children of Ashkenazi background
- Spinal muscular atrophy
- Brain malformations
- Inborn errors of metabolism
- Chromosome abnormalities

In general, if an in utero stroke damages brain tissue but is not life threatening, hypertonia is more likely than hypotonia. All of the conditions listed above have a range of presentations, and the index of suspicion generally increases with the severity of the tone disturbance and with an increasing number of risk factors, such as a positive family history of neurological conditions, multiple physical anomalies, symptoms of a metabolic disorder, and abnormal neurologic function or abnormalities on the neurologic examination. Persistent hypotonia is an important finding, and you would want to keep an expanded differential under consideration.
Past Medical History (Red Flag 2—Growth Delay)

Adam and his family have moved to another state at six months, and his new pediatrician calls you about Adam at his fourteen month visit. You review together that Adam was a full-term newborn born by Caesarean section after an uneventful pregnancy to a 30-year-old gravida3para1 mother, who is 4’11” tall. He grew at the 5th percentile until about a year of age, at which point his height curve started to decelerate. His development is mildly delayed: he meets milestones just outside the range of typical variation. There are no features of regression or atypical behaviors, unusual odors, or decreased eating.

Parental heights are a major predictor of adult height, and it is reasonable to ascribe some growth patterns to familial stature on a multifactorial basis. However, Adam’s mother’s height is below the 3rd percentile, and this is a red flag for a possible autosomal dominant condition.

**Question 3.** Which of the following questions would be most helpful regarding potential underlying genetic conditions? Choose the best answer.

(A) Has Adam had any surgeries?
(B) Are Adam’s immunizations up to date?
(C) How long was breastfeeding continued?
(D) Is Adam in day care? If so, how long has he been in day care?
(E) Does Adam engage in reciprocal play?

You learn that Adam was born with cryptorchidism and that during corrective surgery, increased bleeding occurred. Work-up for a bleeding diathesis was negative. His mother notes that one of his prior pediatricians thought Adam had a heart murmur, but other pediatricians did not confirm this on physical exam. She thinks that he is a little less energetic than her other child, but overall he is doing well and looks like her and her father. She thinks Adam is “fine.”

**Question 4.** Which of the following questions would be most useful to ask before doing a physical exam?

(A) Has Adam had echocardiography?
(B) Was Adam born in a state where newborns are screened for critical congenital heart disease at birth?
(C) Has Adam seen an ophthalmologist?
(D) Does Adam have any birthmarks?
(E) A and B.

You have identified at least 3 potential concerns that may be related to one another by a unifying genetic diagnosis—cryptorchidism, intermittent heart murmur, and increased bleeding. All states are currently investigating or implementing newborn point-of-care screening by pulse oximetry for critical congenital heart disease. There are 7 primary screening targets (hypoplastic left heart syndrome, pulmonary atresia with intact septum, tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, and truncus arteriosus) and 5 secondary targets (coarctation of the aorta, double outlet right ventricle, Ebstein anomaly, interrupted aortic arch, and single ventricle). Less-critical heart anomalies such as pulmonic stenosis may not be picked up by newborn screening. The complications during Adam’s prior surgery and the intermittent murmur suggest the need for further evaluation or referral, especially given the flattening of growth and your growing concern about a familial condition. See the table below regarding the use of the F GENES mnemonic to determine whether further evaluation or referral is necessary.²(p53)
Family History (Red flag 3—positive family history)

Using the SCREEN mnemonic for family history collection, you learn that Adam's mother had an in utero pregnancy loss at 20 weeks with hydrops and that her father died at 50 years of age with a heart condition.

**SCREEN Mnemonic**

<table>
<thead>
<tr>
<th>SC – SOME CONCERNS….</th>
<th>“Do you have any concerns about diseases or conditions that run in your family?”</th>
</tr>
</thead>
<tbody>
<tr>
<td>R – REPRODUCTION…</td>
<td>“Have any family members had problems with pregnancy, infertility, or birth defects?”</td>
</tr>
<tr>
<td>E – ETHNICITY…</td>
<td>“What is your ethnic background? Or, “where were your parents born?”</td>
</tr>
<tr>
<td>E – EARLY DIAGNOSIS, DEATH, OR DISABILITY…</td>
<td>“Have any family members died or became sick at a young age?”</td>
</tr>
</tbody>
</table>

**Question 5.** Which of the following questions would be most helpful in addressing your concerns about being clear that this is likely an autosomal dominant condition in Adam’s family?

(A) Did Adam’s deceased maternal grandfather also have short stature?
(B) Do any of Adam’s other relatives (aunts, uncles, or cousins) have short stature, a heart condition, or both?
(C) Are the father and his blood relatives short, average height, or tall?
(D) Do only Adam’s mother’s brothers have short stature and a heart condition?
(E) All of the above.

Given the history, your focused family history questions should relate to the possible association of short stature and a congenital heart condition running across at least 3 generations of this family. If the maternal grandfather had this condition and if it was autosomal dominant, he would have a 50% chance of passing it on to each of his children, independent of their gender. If the condition were X-linked, he could not have passed it on to his sons (Adam’s mother’s brothers), because he gave his sons his Y chromosome.

In taking the pedigree, you find that Adam has an 18-year-old full sister. She has typical stature, has started her periods, is on the basketball team, is doing well in school, and has many friends.
Question 6. Which of the following genetic conditions that can become clinically evident in adolescents are unlikely given this family history?

(A) Connective tissue conditions, such as Marfan syndrome or Loeys-Dietz syndrome
(B) Turner syndrome
(C) Muscular dystrophy
(D) Adrenoleukodystrophy
(E) All of the above

If Adam has an autosomal dominant condition, his sister could have the same condition. Although you know that genetic conditions can become more apparent at significant transitions in growth and pubertal development, you are most concerned about the apparent heart condition in the family. Certain screening questions might allow you to assess whether an adolescent presentation of such a condition is less likely than presenting at another age. His sister may need further evaluation and genetic counseling. Asking the mother to share a photo of the sister might be helpful in this regard.

Physical Examination (Red flag 4—physical abnormalities)
Physical examination reveals that Adam has low-set, posteriorly rotated ears, a heart murmur, and a broad neck and chest. He looks like his mother. His genitalia appear normal. He says a few words and is walking well. You know you have seen a photo of a child who looks like Adam in a pediatric book that includes syndromes.

Question 7. Which of the following statements is true?

(A) Pediatricians should not use the OMIM.org search function to narrow a differential diagnosis.
(B) Pediatricians should not use the word "genetic" in talking to families, because the term is likely to frighten them. Referral to a geneticist undermines the medical home approach.
(C) The American Academy of Pediatrics needs to develop a fact sheet about referral to a geneticist.

(D) Genetics services need to be integrated into the medical home to provide comprehensive and coordinated care for children and families with inherited conditions.

You have been noting the similarities between Adam and his mother, who is visibly pregnant.

**Question 8.** Given your concern about Adam's health and the family history including an in utero death with hydrops, which of the following would be the best actions to take?

(A) Assume that the mother's obstetrician is similarly concerned
(B) Call a geneticist colleague and ask for triage advice
(C) Ask the mother about her concerns
(D) Call the father to assess his concerns
(E) B and C

Adam's physical findings lead you to consider further evaluation or referral. Given your concern about Adam's health and the family history, including an in utero death with hydrops, you speak with a geneticist colleague, and you both think that Noonan syndrome is likely. Because of concerns about pulmonic stenosis and other cardiac abnormalities in both the mother and Adam, you arrange for a cardiac consultation and get the mother's permission to speak with her obstetrician. The geneticist offers an appointment the following week for Adam.

The geneticist concurs that the clinical features suggest Noonan syndrome when the patient is seen in genetics clinic and plans to order sequential molecular testing for the genetic changes associated with Noonan syndrome.

**Question 9.** Which of the following are important elements of informed consent for genetic testing?

(A) Discussing the purpose and possible outcomes of the test
(B) Discussing the benefits and limitations of the test, including costs
(C) Waiting to discuss family implications until you have the results
(D) B and C
(E) A and B

**Diagnostic Testing (Red flag 5—positive laboratory tests)**

Adam tests positive for a *PTPN11* mutation, which is a missense mutation that accounts for about 50% of cases of Noonan syndrome. Now that you have diagnosed Noonan syndrome in Adam, you will need to collaborate with the geneticist in the family management.

**Question 10.** Which of the following is the most reasonable strategy for following through on family testing?

(A) Test Adam's 18-year-old sister first for the entire *PTPN11* gene.
(B) Encourage the mother to meet with a genetics counselor to discuss testing options for her and potential prenatal diagnosis for her unborn child.
(C) Tell the mother she needs an amniocentesis to test for the whole *PTPN11* mutation.
(D) Test Adam for the other Noonan syndrome–associated genes in the RAS-MAPK pathway for encoding proteins related to signaling transduction.
(E) Offer whole-genome sequencing to Adam’s sister.
Echocardiography indicates that Adam has pulmonic stenosis, which is consistent with his \textit{PTPN11} mutation. Although Noonan syndrome is often the result of new mutation (which would confer a low recurrence risk), Adam’s condition is likely the result of a familial mutation. It is likely related to his maternal grandfather’s heart condition and may be related to the pregnancy loss of the fetus with hydrops.

\textbf{Question 11.} Which of the following actions is not part of the management guidance for Noonan syndrome?

(A) Monitoring growth with consideration of endocrine referral  
(B) Follow-up echocardiograms/EKGs to detect cardiac hypertrophy  
(C) Coagulation screening  
(D) Low-fat, high-carbohydrate diet  
(E) Renal ultrasound  
\textbf{(F) CBCs every 6 months to look for juvenile myelomonocytic leukemia and acute lymphoblastic leukemia}

Actions A–E are generally recommended. Although the risk of juvenile myelomonocytic leukemia and acute lymphoblastic leukemia is 1–2\% in children with Noonan syndrome, the index of suspicion is low, and none of the currently available evidence supports screening with periodic blood counts.

\textbf{Management}

It is important to explain the goals of the genetics evaluation to the family prior to a referral. Primary care providers can help families understand that the major objective is to provide a unifying diagnosis for the child’s findings and to support the family, not to blame them. Genetic referral and collaboration are consistent with the medical home model.\textsuperscript{2} The American Academy of Pediatrics has developed a fact sheet on genetics referral.\textsuperscript{3} Note that families may have looked at online sources prior to visiting your office, and being aware of accessible and reliable resources for them going forward is important.

The potential family diagnosis may have added urgency in the setting of a current pregnancy, but an alarmist approach may undermine follow-through. Seeking to understand the family dynamics and getting advice from a geneticist or genetics counselor with whom you have developed a collaborative relationship can be helpful. The offer, timing, and practical realities of diagnostic genetic testing will likely need to be coordinated.

Understanding the elements of informed consent is important as part of the medical home; misstating any of the elements can impact follow-through. An informed choice with regard to genetic testing is compatible with ethical guidelines. Appropriate family testing should be grounded in informed consent and the up-to-date understanding of the clinical utility of various testing technologies.

\textbf{Summary}

The diagnosis, treatment, and prevention of genetic and or potentially genetic-related disorders requires the astute attention of the PCP in the medical home for potential red flags. It is important for the pediatrician to develop the ability to appreciate when a child has something more than the
usual infection or when something about a child’s growth, development, family history, or physical exam is out of the ordinary. Genetic thinking is important in primary care because the patient may never see the appropriate specialized diagnostician unless he or she is referred by the primary care provider. The pediatrician needs to be able to recognize the rare and unusual presentation of common and uncommon conditions to provide optimal care. Lifelong learning in developing genetic thinking—some might call it developing genetic antennae or genetic eyes and ears—is particularly important in the era of genomic medicine. A red flag may be considered as any clinical finding discovered in the history, physical examination, or laboratory studies that suggests the presence of a genetically influenced disease and that may require further action, such as intervention, counseling, referral, screening, or follow-up. Increasingly, genetic information will be integrated in electronic records and point-of-care tools, and red flags will be integrated into daily thinking and practice.

References

Resources for Parents and Caregivers