Genetic Evaluation of Children With Developmental Disabilities

ACGME Sub-competencies / Developmental Milestones Addressed

**Patient Care:** Gather essential and accurate information about the patient; Make informed diagnostic and therapeutic decisions; Develop and carry out management plans

**Practice-based Learning and Improvement:** Identify strengths, deficiencies, and limits of one’s knowledge

**Professionalism:** Develop awareness of limitations to engage in help-seeking behaviors

**Systems-based Care:** Coordinate patient care within the health system

Overview

One in every 6 children between the ages of 3 and 17 has a developmental disability, a term that refers to impairment in behavioral, physical, learning, and language areas. Because developmental disabilities can affect all ethnic, racial, and socioeconomic groups, pediatricians in all practices will encounter such children. This case will focus on the work-up of a child with developmental disabilities. The case will highlight the importance of a good initial assessment and will demonstrate how understanding a patient’s history can help with a diagnosis.

Learning Objectives

Upon completion of Genetic Evaluation of Children With Developmental Disabilities, residents should be able to

- list genetic syndromes along with environmental factors in a differential diagnosis when working up a child with cognitive delays, other developmental disabilities, or autism,
- use past medical history to establish and narrow a differential diagnosis,
- interpret fragile X syndrome testing results, and
- medically manage a patient with fragile X syndrome.

Case Presentation

**Initial Presentation**

David, a 10-year-old boy, and his mother arrive at your pediatric office for a new appointment. The child was previously seen in another local practice, and his mother is transferring his care to your practice. Before entering the examination room, you look at David’s records and learn that he has been diagnosed with developmental disabilities including an intellectual disability and language
problems. He currently is in special education classes. Besides establishing care, David's mother is most concerned about his intellectual disability.

**Question 1.** Which one of the following is least likely to be the cause of David's developmental disabilities?

(A) Chromosomal abnormality  
(B) Postnatal exposure to lead  
(C) Prolonged inpatient stay as a neonate  
(D) Prenatal exposure to alcohol  
(E) Prenatal exposure to acetaminophen

According to Boyle et al. (2011), from 2006 to 2008, roughly 1 in 6 children in the US was reported to have developmental disabilities. The causes of developmental disabilities can be genetic, environmental, or both. Genetic factors include autosomal trisomies, known genetic syndromes, and previously unknown conditions that are now being identified with advance genomic testing. For children with global developmental delay or a developmental disability like intellectual disability or autism spectrum disorder, microarray testing is now recommended as a first-tier test.

When evaluating a patient with DD, including intellectual disability, it is important to evaluate for prenatal or postnatal causes. For example, extreme prematurity and the associated complications can lead to developmental disabilities. Traumatic brain injuries, including near drownings and motor vehicle accidents, cause disabilities. Postnatal and prenatal exposures to various substances are additional causes of developmental disabilities. For example, severe lead poisoning during childhood has a well-documented association with failure to reach developmental milestones. Fetal alcohol spectrum disorders are a direct result of maternal alcohol use during pregnancy and can lead to deficits ranging from memory and attention problems to communication and learning issues. Certain medications taken during pregnancy (such as valproate) and environmental exposures (such as viral infections) have also been associated with developmental disabilities. However, there is no known association between developmental disabilities with acetaminophen.

**Question 2.** Which of the following chromosomal abnormalities is least likely to be the cause of David's condition?

(A) A gene mutation  
(B) A microdeletion  
(C) A microduplication  
(D) Full monosomy  
(E) Full trisomy

You have not yet seen David, so a myriad of possibilities exist. Both chromosomal aneuploidy (such as Down syndrome) and contiguous gene deletion and duplication syndromes (such as velo-cardio-facial syndrome and Williams syndrome) can lead to developmental disabilities. Full monosomies are almost always lethal prenatally and spontaneously miscarry. If an obvious chromosomal phenotype such as a chromosomal aneuploidy is present, karyotype analysis is appropriate. If a microdeletion or microduplication syndrome is suspected, microarray testing is recommended. In the Online Mendelian Inheritance in Man database (OMIM), there are more than 1,000 entries associated with a form of developmental disability.
**Past Medical History**

After introducing yourself to David and his family, you begin to learn more about him. His mother had an uncomplicated pregnancy. There were no teratogenic exposures, and ultrasounds were normal throughout the pregnancy. Because there were no specific indications, no genetic testing was done prenatally. David’s mother was 22 years old at the time of his delivery. He was born at full term without any complications. He was placed in the well-baby nursery and left the hospital within 2 days. David’s mother has a copy of his normal newborn screening results.

**Question 3.** Which of the following scenarios in David’s past medical history would be the strongest indication of a genetic abnormality?

(A) David had an umbilical herniation that resolved spontaneously.
(B) **David had a history of hypotonia and speech delay, requiring early intervention.**
(C) David had a stutter during childhood, but it resolved over time.
(D) David was hospitalized for asthma twice but never required intubation.
(E) David was noted to have epicanthal folds during his 2-week-old well-child visit.

No minor or major anomalies were reported in the newborn period. Minor congenital anomalies are defined as subtle changes in appearance and structure that do not cause morbidity or mortality. Examples include umbilical hernias and epicanthal folds. Umbilical herniation is commonly seen in infants and often resolves on its own during the first 3 years of life. Epicanthal folds, that is, folds of eyelid skin that cover the inner corner of the eye, are common in individuals of Asian descent. Epicanthal folds alone are not an indication of a genetic syndrome. However, if David had a history of hypotonia and speech delay, this would raise the possibility of a genetic abnormality, and it would be important to ask his mother more questions related to these symptoms. Specifically, when did the hypotonia begin? When was the speech delay detected? Do any other family members have hypotonia or speech delay similar to David?

Other than 2 admissions for asthma (neither requiring intubation) when he was 4 years old, David has been physically healthy and has not had any surgeries. His only medication is albuterol as needed. David did require early intervention for a global developmental delay that required occupational, physical, and speech therapy. Currently he is in special education classes. Although there have been improvements with the physical and occupational therapy, David has a hard time communicating and cannot read.

**Question 4.** Given the above history, which of the following documents would be helpful to review?

(A) David’s most recent CBC and basic metabolic panel
(B) David’s most recent note from his asthma admission
(C) **David’s most recent individual education program (IEP)**
(D) David’s most recent report card, to see his improvements over the year
(E) David’s up-to-date vaccination record

Although a recent CBC and basic metabolic panel are important pieces of information to have for David’s record, nothing in the history suggests anemia or an electrolyte imbalance. Obtaining these test results would provide only minimal help in addressing concerns about David’s developmental disabilities.
From the history, his asthma seems well controlled, and no major medical condition has affected David physically. Because David's asthma admissions occurred more than 6 years ago, the admission note is unlikely to provide insight into David's current issues.

David's learning difficulties are significant. Though his mother believes the therapies are helping, review of his IEP would be useful for determining specifically what therapies David is receiving and evaluating his progress toward the established goals. Evaluation of the IEP can give a medical provider a better understanding of David's disabilities. David's report card would give only the numerical or letter grades for his classes and possibly some teacher comments; it would not be as thorough as the IEP evaluation and assessment.

Vaccinations, contrary to popular belief, are not associated with developmental disabilities. His vaccination record is important for his general health but again would not help with the work-up of David's school difficulties and developmental disabilities.

**Family History**

David's mother states that she is concerned about his future. She discloses that there is a family history of developmental disabilities. His 22-year-old maternal uncle, Theodore, who was born at 40-weeks gestational age, has a diagnosed intellectual disability and cannot care for himself. His past medical history is negative for any acquired conditions.

Children born prematurely can develop "cerebral palsy," a broad term that describes a group of nonprogressive but permanent neurological disorders that begin in infancy or early childhood. Some cases of cerebral palsy stem from intrauterine developmental abnormalities, hypoxic events before or during birth, and complications in the perinatal or childhood period. Cerebral palsy is more likely to result from intrauterine and perinatal complications than from an underlying genetic condition.

The fact that a maternal uncle has an intellectual disability should be a red flag to the pediatrician, and increased attention to the family history is necessary. Did Theodore develop the intellectual disability after a traumatic event, or did he always have it? Were any motor delays involved? Did he have a regression of development? A family history of developmental disabilities suggests that there may be a strong genetic factor that is worth exploring.

David's mother states that David's maternal aunt, Silvia, has no developmental disabilities but is being evaluated by a fertility specialist. She currently has two children with developmental disabilities. Sarah (age 8) was diagnosed with a learning disability, and her brother, John (age 18 months), has a speech delay and is currently being evaluated for early intervention.
**Pedigree**

Question 5. Given the pedigree, what is the most likely form of inheritance?

(A) Paternally inherited  
(B) Autosomal dominant  
(C) Autosomal recessive  
(D) X-linked  
(E) Cannot be determined from the information provided

Because the family members mentioned are from the mother’s side of the family, a paternally inherited disorder can be ruled out.

If a disorder were autosomal dominant, each generation would be affected with an equal distribution between the sexes. Though multiple generations are affected, David’s mother and David’s aunt do not seem to suffer from the same developmental disability as the males in the family. In addition, the absence of male-to-male transmission makes an autosomal dominant disorder less likely than other modes of inheritance.

If a disorder were autosomal recessive, we would expect multiple individuals in the same generation to be affected with an equal distribution between the sexes. Because so many generations seem to be affected with developmental disabilities and because there is no history of consanguinity (which would increase the likelihood of an autosomal recessive disorder), an autosomal recessive disorder is less likely than another mode of inheritance.

When a disorder is X-linked, the distribution of affected individuals between the sexes is typically unequal. In an X-linked disorder, males are more likely affected than females because males have only one X chromosome. In females, the X chromosome carrying the mutation can be silenced (owing to X inactivation), and fewer phenotypic manifestations can arise. Given the family history, an X-linked disorder seems to be the most likely possibility.
**Physical Examination**

During the physical exam, David is cooperative. The most striking findings include a long face, prominent ears, and a withdrawn personality.

**Question 6.** From David’s physical exam and the information already provided, which condition is most likely?

(A) Fragile X  
(B) Marfan syndrome  
(C) 22q13 deletion  
(D) Velocardiofacial syndrome

A long face, prominent ears, and a withdrawn personality are some of the hallmark features of fragile X syndrome. The facial features of patients with fragile X become more prominent with age, so David can have a prominent jaw as well. Male children with fragile X syndrome tend to have motor and speech delays, which is also consistent with David’s developmental delays as an infant and his current developmental disabilities.

**Question 7.** Given your suspicion of a genetic syndrome, what else would you look for on the physical exam?

(A) Strabismus  
(B) Pectus excavatum  
(C) Hypermobility  
(D) Macro-orchidism  
(E) All of the above

Because fragile X syndrome is on the differential diagnosis, special attention should be given to some aspects of the physical exam. Children with fragile X syndrome can have eye abnormalities such as strabismus, so David will need a thorough eye exam. Children with fragile X syndrome can also have pectus excavatum. Mitral valve prolapse has been noted in fragile X syndrome, mostly in adults. The heart should be carefully auscultated for murmurs. Many children with this condition have connective tissue abnormalities including pes planus, hyperextensible joints (particularly in the fingers), and smooth, velvety skin. During the physical exam, it is important to check the child’s joints for hypermobility, back for scoliosis, and feet for pes planus. Examination for hernias is also important.6

A common physical abnormality in fragile X syndrome is macro-orchidism, so the child’s testicular volume should be documented with a Prader orchidometer, an inexpensive tool consisting of a chain of 12 numbered beads that correlate to testicular volumes ranging from 1 to 25 mL. Normally prepubertal testicular volume is 1–3 mL, pubertal testicular volume is 4–12 mL, and adult testicular volume is 15–25 mL. In teenagers and adults with fragile X syndrome, testicular volume is around 50 mL.6

**Diagnostic Testing**

Because of your suspicions about fragile X syndrome, you send David to the local geneticist. David and his mother return in 1 month, right after their visit with the geneticist, with a copy of David's genetic testing results showing 250 CGG repeats in exon 1 of the *FMR1* gene.
The vast majority of patients with fragile X syndrome have CGG trinucleotide repeat expansion in exon 1 of the FMR1 gene, which is located on the X chromosome. This gene encodes fragile X mental retardation protein (FMRP), which is found in many different cell types but is present at high levels in neurons. Normally, the gene has 4–44 CGG repeats. A gene with 45–54 CGG repeats is considered to show intermediate expansion (“gray zone”), and a gene with 55–200 CGG repeats is referred to as a premutation. A person, like David, whose FMR1 gene has more than 200 CGG repeats (full mutation) receives a molecular diagnosis of fragile X syndrome. When there are more than 200 CGG repeats in exon 1 of FMR1, the gene promoter undergoes hypermethylation, which effectively turns off the gene; that is, the gene product is not expressed.\(^7\)

**Question 8.** What are the diagnostic tests for fragile X syndrome?

(A) Karyotyping and polymerase chain reaction (PCR)
(B) Karyotyping and Southern blotting
(C) Karyotyping and Western blotting
(D) **PCR and Southern blotting**
(E) PCR and Western blotting

The 2 most common molecular tests used to diagnosis fragile X syndrome are PCR and Southern blotting which utilize target mutation analysis. PCR is used to amplify the DNA containing the CGG repeats, and then undergoes capillary electrophoresis to determine the number of repeats. PCR is more sensitive for alleles with fewer than 120 CGG repeats so this test can detect normal alleles, intermediate expansion, and some premutation expansion. If the PCR results are concerning for an expansion, a Southern blot can be done. Southern blotting detects differences in DNA fragment lengths after the DNA has been treated with restriction enzymes and then run on a gel. Fragments of an FMR1 gene with the normal number of CGG repeats will travel further down the gel than fragments of a gene with the fragile X syndrome premutation or full mutation. Southern blotting can also detect methylation status of the DNA. Together, PCR along with Southern blot analysis is the gold standard for molecular diagnosis of Fragile X syndrome.\(^7\)

Karyotyping reveals the total number of chromosomes and the banding patterns of the chromosomes in a single cell. Because fragile X syndrome is caused by a trinucleotide expansion in a specific gene and depends on the number of repeats, it will not be seen on a simple karyotype.

**Management**

Now that David has a diagnosis, you use Health Supervision for Children With Fragile X Syndrome, published by the American Academy of Pediatrics, as a framework as a for health supervision and anticipatory guidance during the child's routine appointments.\(^6\)

**Question 9.** According to the AAP guidelines, what can be said in terms of anticipatory guidance?

(A) Anxiety or obsessive-compulsive disorder is not typically seen.
(B) School therapies should be reduced in frequency because of his genetic condition.
(C) Macro-orchidism is a sign of precocious puberty, and further evaluation is necessary.
(D) **Scoliosis may develop, but surgical intervention is not usually necessary.**
(E) Enuresis is common but cannot typically be controlled with medication.

More than 50% of children with fragile X syndrome have behavioral issues. Anxiety is frequently seen in these children, much of which stems from social situations. Obsessive-compulsive disorder
is also commonly seen. Adaptive management training at school and in the home may alleviate some of these behaviors.

Regardless of the patient’s age, one should review any interventions the child is receiving for cognitive, motor, speech, and language deficits. Because the full mutation leads to cognitive deficits, it is imperative that the correct interventions be given in school to help David meet his fullest potential. Having a genetic condition should not prevent a child from receiving services or therapies.

Because David is 10 years old, specific parts of the physical exam should be documented. Measurement of testicular volume and assessment for hernias are important to note. In children with fragile X syndrome, macro-orchidism can begin to be seen by the age of 9, although it is usually not noticed until puberty. Note that macro-orchidism is not a sign of precocious puberty. However, precocious puberty has been noted in females who carry the full mutation, so looking for signs of development and documenting Tanner staging are key. Children with fragile X syndrome can develop scoliosis and mild cardiac abnormalities, so a careful exam should be done at each visit.6

Another common finding in children with fragile X syndrome is enuresis. If there is a history of recurrent urinary tract infections or if there is reflux or a structural anomaly of the urinary system, appropriate evaluations or referrals should be done.

**Question 10.** Given David’s genetic test results regarding fragile X syndrome, what other actions are recommended for David and his extended family?

(A) Order whole exome sequencing on his cousin, Sarah  
(B) Counsel females of reproductive age on the paternal side of the family to receive genetic testing  
(C) Counsel males of reproductive age on the maternal side of the family to receive genetic testing  
(D) **Counsel family members of reproductive age on the maternal side of the family to receive genetic testing**  
(E) No further actions are recommended

As mentioned above, fragile X syndrome is X linked. David’s X chromosome was inherited from his mother. Therefore, neither David’s father nor any of the paternal family members need to be referred for genetic testing. However, David’s mother should be seen by a geneticist or genetic counselor. She may be a carrier of a premutation or a full mutation. Females who are heterozygous for the full mutation may have some of the behavioral features but usually have milder developmental impairments. In addition female carriers of the premutation have a 21% chance of developing primary ovarian insufficiency. It has been noted that 5–10% of women with primary ovarian insufficiency may conceive.6 If David’s mother is a premutation carrier, she is also at risk for fragile X-associated tremor/ataxia syndrome, which is characterized by intention tremor and late-onset progressive cerebellar ataxia. By going to a geneticist, David’s mother can discuss these possibilities and be referred to the appropriate specialists if necessary.

Given that David has fragile X syndrome, the family may want to find out whether David’s uncle Theodore, who has the intellectual disability, also has fragile X syndrome. In addition, David’s Aunt Silvia, who is having fertility issues and has 2 children with developmental disabilities, may have a premutation. If Aunt Silvia is a premutation carrier, it could lead to a diagnosis for her children.
David's test results affect not only him but also his entire family. On the basis of the results of the genetic tests, David's family will have to decide whether they want to inform other family members about this genetic information, and then each family member (or his or her guardian) will have to decide whether to pursue genetic testing.

**Summary**
In the evaluation of a patient with developmental disabilities, the “thinking genetically” approach can be quite useful for the physician and helpful for the patient and family. The paradigm of diagnosis, treatment, and prevention directs the primary care provider to consider appropriate evaluation methods, as well as specific supportive interventions that will decrease the impact of the diagnosed condition, both now and in the future.

**Diagnosis**
When working with a child with developmental disability, collecting as much family history and past medical history as possible is important because this information will help narrow down the differential diagnosis of the potential causes of the developmental disability. In David’s case, his family history, lack of exposures during his prenatal course and early development, past medical history, and physical exam all played a role in his fragile X diagnosis.

**Treatment**
The AAP has developed health supervision guidelines to assist pediatricians in caring for patients with fragile X syndrome.6

**Prevention**
The diagnosis of fragile X syndrome is just the start for a child and his or her family. The pediatrician must remember that a diagnosis of this syndrome in a child also affects the other family members. The pediatrician and the geneticist must work together in counseling these families and suggesting that family members who are at risk for the condition (or a premutation) consider getting genetic testing. Attention to these matters is critical to the primary care provider who is managing the patient within the medical home context.

**References**

Resources for Parents and Caregivers