Fragile X Syndrome

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Key Points

- Fragile X syndrome is the most common single-gene cause of hereditary mental retardation. It is caused by a CGG trinucleotide repeat expansion in the *FMR1* gene on the X chromosome.
- Any child with developmental delay of unknown etiology should be considered for fragile X syndrome testing. Family history of mental retardation and/or suggestive physical features can make the diagnosis more likely.
- A diagnosis of fragile X syndrome can inform the family about a child's prognosis and enable the child to receive needed services; this information also informs the family about their future reproductive risk as well as risk to other family members.

Learning Objectives

Participants will be able to:

- Describe the physical and behavioral features of individuals suggestive of fragile X syndrome;
- Explain the reproductive implications of identifying a full mutation versus a premutation in the *FMR1* gene;Discuss the implications of a diagnosis of fragile X syndrome for the child and family.

Family History Issues

Fragile X syndrome is inherited as an X-linked disorder. Family history is often unremarkable. In some families, however, males on the maternal side of the family, such as maternal uncles or male cousins, have mental retardation. Females can show milder features of fragile X syndrome, including developmental disability.

Red Flags 

The diagnosis of fragile X syndrome is suspected in males and females with otherwise unexplained developmental delay or mental retardation. Certain behavioral features (hyperactivity, social anxiety, perseverative speech) increase concern for fragile X syndrome. Affected males may have characteristic facial features such as a large head circumference, long face, prominent forehead, large ears, and prominent jaw. But these features are not always present in young children with fragile X syndrome. Females can have similar physical and behavioral characteristics but typically have milder involvement.

Case 16. A Two-Year-Old Boy with Developmental Delay

A continuity clinic resident presents Chad, a two-year-old boy who has come for well child care. At Chad's last well child visit, at 15 months of age, the history and physical examination were normal, but he was not talking. Chad still has no expressive language. He appears to hear normally and follows simple commands. His gross and fine motor development appear normal for his age. He is described as shy. Parents note that he is not communicative with other children or adults and consistently avoids eye contact. He is frequently irritable and hyperactive at home.

Neonatal history. Chad was the 3.5-kg product of a normal pregnancy and delivery. His mother had no history of prenatal illness, medication use, alcohol use, or substance abuse. Chad's Apgar scores were 8 at one minute and 9 at five minutes. His neonatal course was notable only for a peak bilirubin of 10 on day four of life. Newborn screening results were normal.

Family history. Chad has a healthy four-year-old sister, Kara. Kara is also shy but has been doing well in day care. Kara began to use single words at about 15 months of age and has no evidence of developmental problems. Chad's father, Jack, is healthy. His mother, Monica, is 26 years old and in good general health. She is 12 weeks pregnant. She has a history of depression and anxiety disorder but is currently not in therapy or on medication. Monica is the youngest of three children. Her older brother was "slow" in school. He was killed in a motor vehicle accident when Monica was a teenager. Her sister left home at 16 years of age and has since had only intermittent contact with Monica. She is healthy and married but has no children to Monica's knowledge. Monica's parents are in reasonable health; at age 66, her father has hypertension and degenerative joint disease and at

age 60, her mother has diet-controlled diabetes mellitus.

Social history. Monica works in environmental services at a downtown office building. She struggled academically in school, attaining only a 10th grade education. Jack works as a backhoe operator in a local construction company. He also struggled in school but graduated from high school. Monica and Jack are happily married and there is no history of alcohol or substance abuse or domestic violence. The family's health insurance is provided by Medicaid, although Jack will soon be eligible for coverage through his employer.

Physical examination. Chad is at the 20th percentile in weight, 30th percentile in height, and 90th percentile in head size. These measures are consistent with previous points on the growth chart. While sitting on his mother's lap, he is withdrawn and resists being examined. Except for serous otitis media, his physical examination is normal.

Clinical Care Issues

Developmental delay

Developmental disability occurs in 5-10% of children and global developmental delay in about 1-3% [Shevell et al 2003]. Global developmental delay is defined as significant delay in at least two developmental domains (motor, language, cognition, social/personal, or activities of daily living) [Shevell et al 2003] Developmental delay has many causes, including infections, toxic/teratogen exposure, perinatal hypoxia/ischemia, and a variety of genetic conditions [Battaglia et al 1999]. In about 20-30% of global developmental delay cases, no cause can be identified after routine workup [Battaglia et al 1999, Shevell et al 2003].

Genetic causes of developmental delay

Genetic conditions associated with developmental delay include chromosomal abnormalities, inborn errors of metabolism, and other single-gene disorders. Identification of a genetic cause provides information about prognosis and recurrence risk (the risk that the condition will occur in subsequent children). A physical examination may reveal findings that point to a genetic diagnosis. For example, Down syndrome has characteristic physical findings (see Case 22, Red Flags), and the combination of developmental delay with two or more dysmorphic features increases the likelihood of a chromosomal

disorder.

Important elements of the genetic workup include routine cytogenetic studies (diagnostic yield: 3.7%), screening for subtelomeric chromosomal rearrangement (6.6%), fragile X molecular testing (2.6%), and in females, screening for Rett syndrome [Shevell et al 2003]. Metabolic studies have a low diagnostic yield when previous newborn screening was negative, but should be considered if there are findings suggestive of a specific disorder (or a family history of a specific disorder), or if newborn screening was not done or included few tests. Other non-genetic workup commonly recommended includes neuroimaging, lead screening, and visual and auditory screening [Shevell et al 2003].

Workup in this case

Chad's delay in expressive language and possible delay in social interactions are an indicator for additional workup. His normal prenatal and birth history argue against teratogenic or perinatal causes for his developmental problems. His normal newborn screen makes a metabolic disorder unlikely.

His family history is significant for a maternal uncle with mental retardation and learning problems in his mother. This family history points to the importance of assessing Chad for physical findings compatible with known X-linked causes of developmental delay, such as fragile X syndrome.

However, even in the absence of family history, fragile X syndrome should be considered, as the most common form of inherited developmental delay. Workup should include fragile X testing unless the physical examination and history suggest another specific cause of developmental delay. This is true even when, as in this case, physical findings of fragile X are absent, because the physical signs of fragile X are often not present in a young child.

A genetic consultation, for careful review of physical findings and family history, may be helpful in determining the value of other genetic workup, notably chromosomal studies. Developmental disability can be multifactorial, without a specific identifiable cause. In Chad's case, both parents have struggled academically and his mother has a history of anxiety and depression. Social factors could have contributed to his speech delay and social behavior. The genetic workup has the goal of identifying (or ruling out) specific causes that have implications for prognosis and inheritance.

Fragile X syndrome

Individuals with fragile X syndrome have normal growth, appearance, and birth. However, developmental milestones are typically delayed, particularly speech development. Between the toddler and preschool years, certain behaviors may become noticeable, such as hyperactivity, short attention span, and autistic-like behaviors (difficulty adjusting to change, poor eye contact, hand biting or flapping, hypersensitivity to sound or light). Moderate to severe learning problems are seen in boys with fragile X syndrome. About 50% of female fragile X syndrome carriers have learning problems or mental retardation.

At age two years, Chad might exhibit some of the physical characteristics of fragile X syndrome, such as a large head. However, other features of fragile X syndrome, such as a prominent forehead, prominent jaw, and large ears, are unlikely to be present at his age. After puberty, these features, as well as large testes, are more likely to be present. Chad has also shown some of the behavioral characteristics associated with fragile X syndrome, such as delayed speech, poor eye contact, and hyperactivity.

Risk Assessment

Any child (male or female) with delay of speech, language, or motor development of unknown etiology should be considered for fragile X syndrome testing, especially in the presence of a positive family history of mental retardation, a consistent physical and behavioral phenotype, and absence of structural abnormalities of the brain or other birth defects [Curry et al 1997].

The prevalence of fragile X syndrome is about one in 5000 males and is the most common cause of inherited mental retardation. It is estimated to be present in 3-6% of unselected males with developmental disability. About 40% of X-linked mental retardation is due to fragile X syndrome. In this case, X-linked mental retardation is suspected because Chad's maternal uncle had mental retardation and Chad's mother has learning difficulties.

Genetic Counseling and Testing

Genetic testing for fragile X syndrome

The *FMR1* gene contains a region in which repeated copies of a 3-nucleotide sequence, CGG, occur. The normal number of CGG repeats in the *FMR1* gene is fewer than 59. Fragile X syndrome is caused by a CGG trinucleotide repeat

expansion, in which many more copies of CGG are present. The presence of developmental disability is determined primarily by the number of CGG trinucleotide repeats present, but inheritance is complex [Saul & Tarleton 2004, McIntosh et al 2000].

A "full" mutation is the presence of more than 200 CGG repeats; 100% of males with this number of repeats have developmental disability. In females the effect is less predictable: a usually milder form of developmental disability occurs in approximately 50% of females.

When an intermediate number of repeats is present (59-200), the person is said to have a "premutation." People carrying a premutation generally have normal intellect (rare cases of mild impairment have been reported). However, when a premutation is transmitted by the mother, it may expand to a full mutation (see *GeneReview*: Fragile X Syndrome, Table 4). Rarely, contractions (reduction in the number of CGG repeats with gene transmission from parent to child) may occur. Additionally, methylation status of the gene (i.e., inactivation) can play a role in the degree of learning impairment. Usually, methylation is present with full mutations and absent with premutations.

Clinical testing is available to test for the number of CGG repeats in the *FMR1* gene. About 1% of patients with fragile X syndrome have a different molecular defect, e.g., a specific mutation affecting the DNA sequence in another region of the *FMR1* gene. Thus, testing for the trinucleotide repeat is about 99% sensitive and 100% specific.

Assuming that a diagnosis of fragile X syndrome is made in this case, it has important implications for the patient and his family, providing them with:

- An explanation for Chad's developmental delay. Providing a specific diagnosis is often of value in and of itself. It is also the likely explanation of the mother's learning difficulties and those of her deceased brother. The diagnosis of fragile X syndrome may lead to feelings of guilt, but may also relieve guilt and anxiety if either parent had been concerned about some other cause for which he or she might have felt responsible.
- Prognostic information. The diagnosis of fragile X syndrome will help the family to understand that Chad will have permanent disability rather than to hope unrealistically that he will recover from his "delay." The developmental disability seen in fragile X syndrome is typically moderate rather than severe. Often the phenotype includes behavioral

problems such as hyperactivity, poor eye contact and withdrawn social behavior, perseverative speech, and in extreme cases, autism.
- Access to educational and/or social services.
- Information about genetic risks for other family members. Other family members at risk of having this condition or of having children with this condition may consider molecular genetic testing.

Optimal testing strategy for this family

If Chad is tested and is found to have an expansion of more than 200 CGG repeats in the *FMR1* gene, recurrence risk for future siblings becomes a concern, as does the status of his older sister (see Genetic testing of siblings). Evaluating these questions would require confirmation of his mother's genetic status, i.e., whether she carries a premutation or a full mutation. Because Chad's mother is currently pregnant, it would also be important for her to know that testing options for fragile X syndrome include prenatal diagnosis. If she and her husband wished to pursue prenatal diagnosis in this pregnancy, testing would need to be expedited.

If Chad's mother has a full mutation, the risk of her transmitting the full mutation to her offspring is 50%. For a male with a full mutation, the risk for developmental disability is 100%; for a female with a full mutation, the risk is 50%, and the disability is usually milder than in a male. If Chad's mother carries a premutation, the risk that it would expand to a full mutation is related to the number of repeats in the premutation, with the risk higher when the premutation has more CGG repeats (see *GeneReview*: Fragile X Syndrome, Table 4).

Because inheritance of fragile X syndrome is complex, Chad's mother and father are likely to benefit from genetic counseling before pursuing testing. Genetic counseling would provide them with the opportunity to learn about fragile X syndrome as well as about testing options available to them. In addition to considering recurrence risk for Chad's parents, genetic counseling would include the implications of a fragile X syndrome diagnosis for other family members, particularly those of reproductive age. For example, Monica's older sister would need to be informed that her risk of being a carrier is 50%. Other female relatives on Monica's mother's side, such as cousins, may also be carriers.

Genetic testing of siblings

Chad's sister Kara, currently age four years, reportedly has normal

intelligence and although she is said to be shy, she has not exhibited any of the same learning or behavioral problems as Chad. Based on this information, genetic testing for diagnostic purposes does not appear to be indicated in her case. However, she could carry a full mutation or premutation, and could be at risk of having affected children later in her life. The questions of when to test and when to inform a child about a genetic reproductive risk are major concerns to parents.

Some position papers address these issues [ACMG/ASHG 1995, NSGC 1995]. These statements raise concerns about potential harms of carrier testing in childhood, such as damage to self-esteem, distortion of the family's perception of the child, loss of future adult autonomy and confidentiality, and discrimination (in access to insurance, employment, or education). However, there may also be some benefits to carrier testing in childhood, such as enhanced communication within the family, allowing the child some time to adjust to the genetic risk, and resolution of parental concerns about carrier status.

These issues should be discussed as part of genetic counseling. It may be appropriate to encourage Chad's parents to delay testing of Kara, unless she demonstrates educational or other developmental problems that indicate a need for diagnostic testing.

Interventions

Care for fragile X syndrome consists of supportive therapies aimed at treating the particular behavioral and developmental problems present in the affected individual. Therapies commonly used include behavioral or pharmacologic treatment for behaviors associated with fragile X syndrome, and services such as special education, occupational therapy, and speech therapy. Ongoing research is aimed at identifying educational and pharmacologic interventions specific to fragile X syndrome (See National Fragile X Foundation).

Ethical/Legal/Social/Cultural Issues

Finding out that a child has a condition associated with serious learning problems can be difficult for parents, particularly when the cause of the problem is hereditary. Chad's mother will learn that Chad's problems are a result of a gene inherited from her, and she may feel guilty, or her husband and/or his family may blame her. The stresses may be compounded by learning about the broader family implications of the diagnosis. In learning

about the inheritance of fragile X syndrome, Chad's mother will be informed of the cause of her own learning disabilities and the likely cause of her deceased brother's learning problems. She and her husband will also learn that the current pregnancy is at risk for fragile X syndrome.

Taking in all the risk information that follows from the diagnosis of fragile X syndrome may be difficult for parents. In this case, Chad's mother's history of depression and anxiety may put her at increased risk for psychological problems following the diagnosis. The couple may currently be without sufficient health insurance, and may need both supportive counseling and financial assistance.

Resources

- **Mental Retardation Association of America, Inc (MRAA)**
  211 East 300 South, Suite 212
  Salt Lake City, Utah 84111
  Phone: 801-328-1574

- **American Association on Mental Retardation (AAMR)**
  444 North Capitol Street NW, Suite #846
  Washington DC 20001
  Phone: 202-387-1968; 800-424-3688
  Fax: 202-387-2193
  Email: aamr@access.digex.net

- **FRAXA Research Foundation**
  Newsletter: FRAXA Research Foundation Newsletter. Subscription through FRAXA
  45 Pleasant St
  Newburyport, MA 01950
  Phone: 978-462-1866
  Fax: 978-463-9985
  Email: info@fraxa.org

- **National Fragile X Foundation**
  Newsletter: The Foundation Quarterly. Subscriptions through National Fragile X Foundation
  PO Box 190488

San Francisco, CA 94119-0488
Phone: 800-688-8765
Fax: 925-938-9315; 925-938-9300
Email: natlfx@FragilX.org

- **NCBI Genes and Disease**
  Fragile X syndrome

- **National Library of Medicine Genetics Home Reference**
  Fragile X syndrome

- **GeneTests Online Medical Genetics Information Resource**

- ***GeneReview:* Fragile X Syndrome**

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