AMERICAN ACADEMY OF PEDIATRICS

Health Supervision for Children With Fragile X Syndrome

Committee on Genetics

This set of guidelines is designed to assist pediatricians in caring for children with fragile X syndrome confirmed by DNA analysis (Table). Occasionally pediatricians are called on to advise a pregnant woman who has been informed of a prenatal diagnosis of fragile X syndrome. Therefore, guidelines are also offered for this situation.

Fragile X syndrome is usually diagnosed during childhood and is characterized by developmental delay or mental retardation, characteristic physical features, and abnormal behavioral patterns.[1,2] The distinctive fragile site on the X chromosome was first described in 1969 as a discontinuous site on the long arm of the X chromosome present after cell culture under folate-deficient conditions. In 1977 the relationship of this site to X-linked mental retardation was noted, and fragile X syndrome began to be defined. Since that time, the cytogenetic, molecular, and clinical features of the condition have been more clearly defined,[3] and it is now recognized as the most common hereditary cause of mental retardation. Its frequency has been estimated to be approximately 1 per 2500 to 1 per 1250 males and 1 per 5000 to 1 per 1600 females.

The phenotype of fragile X syndrome in males often has a number of distinctive, recognizable features, including developmental delay or mental retardation, a prominent forehead, a long, thin face and a prominent jaw that appear late in childhood or early adolescence, large protuberant and slightly dysmorphic ears, and the presence of or ultimate development of macro-orchidism. This phenotype can be very subtle, is not always apparent, and becomes more identifiable with age.[2] Other features occasionally seen include a cleft palate, strabismus, serous otitis, joint laxity, dislocated hips, club feet, seizure disorders, and mitral valve prolapse. Particular behavioral patterns often seen include hyperactivity, aversion of gaze, manneristic behavior, hand mannerisms or stereotypies, and perseverative speech. In females,[4-6] there is great variability in the phenotype, including some or all of the craniofacial features seen in males and variable intellectual involvement ranging from normal intellectual functioning to profound mental retardation. Some degree of intellectual impairment is seen in 30% to 50% of heterozygous females. They may also have disorganized thinking, social anxiety, feelings of isolation, and poor self-image.[1-4]

The cytogenetic feature of fragile X syndrome is the presence of a fragile site at band Xq27.3, which is expressed under conditions of folate deficiency during cell culture.[1] This feature is of interest but is no longer considered sufficiently precise for clinical diagnostic use. The genetic locus, designated *FMR1*, has been mapped to chromosome Xq27.3, the same position as the fragile site. The molecular disorder has been defined as an expansion of a series of repeats of the trinucleotide CGG. Between six and about 50 sets of this CGG trinucleotide occur in the 5′ untranslated region of the normal *FMR1* gene.[7]

In fragile X mental retardation, the number of repeats is expanded, and when the number of repeats is greater than about 200, the CG nucleotides become methylated, the gene is turned off, and its protein is not made. This situation is termed the "full mutation." Males with the full mutation usually have the phenotype of fragile X mental retardation. About two thirds of females with the full mutation have some degree of mental retardation. Diversity in the phenotype is related to the number of repeated CGG sets. When the number of repeats is between 50 and 200, the phenotype is variable; this is termed the "premutation." Current information suggests that individuals who have the premutation are unaffected. Expansion of the number of repeats occurs during meiosis in females. Thus, a female may carry a premutation and be clinically unaffected. The CGG repeats in her *FMR1* gene can undergo expansion during meiosis to be passed on to a son who will have the full mutation and an affected phenotype. A male carrying the premutation is known as a "transmitting" male. Such a transmitting male will pass the premutation to all his daughters. Although the daughter who carries a premutation will have a normal phenotype, her *FMR1* gene may undergo an expansion that makes her at risk for having sons with the full mutation and an affected phenotype.[8-10] DNA-based molecular methods can provide precise diagnostic information for most such families.[1,4,5]

Genetic counseling and carrier detection for sib-

The recommendations in this policy statement do not indicate an exclusive course of treatment for children with genetic disorders but are meant to supplement anticipatory guidelines available for treating the normal child provided in the American Academy of Pediatrics publication, *Guidelines for Health Supervision*. They are intended to assist the pediatrician in helping children with genetic conditions to participate fully in life. Diagnosis and treatment of genetic disorders are changing rapidly. Therefore, pediatricians are encouraged to view these guidelines in light of evolving scientific information. Clinical geneticists may be valuable resources for the pediatrician seeking additional information or consultation.

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TABLE. Fragile X Syndrome: Guidelines for Health Supervision*

	Age					
	Infancy, 1 mo–1 y			Early Childhood, 1–5 y	Late Childhood, 5–13 y	Adolescence to Early Adulthood, 13–21 y or Older
	Newborn	1–6 mo	6–12 mo			
Examination						
Ocular	○†	○	○	○	○	○
Ear, nose, throat		○‡	○	○	○	○
Skeleton	○§				●	●
Cardiac	●	●	●	●	●	●
Measure testes				●	●	●
Development	●	●	●‖	●	●	
Neurologic			●	●¶	●#	●#
Behavior	●**	●	●	●	●††	●††
Anticipatory guidance						
Genetics	●‡‡	●		●	●§§	●§§
Psychosocial	●‖‖	●	●	●	●	
Support groups	●	●	●	●	●¶¶	●¶¶
Early intervention, physical and therapy		●	●	●	●##	●##
Behavior	●	●	●	●	●	●
Education				●***	●†††	●†††

* Assure compliance with the American Academy of Pediatrics Recommendations for Preventive Pediatric Health Care. ● indicates to be performed; and ○, objective, by standard testing.
† Strabismus may occur anytime between birth and 4 years of age.
‡ Serous otitis can occur throughout childhood, and the resulting hearing loss can further impair speech development. Pressure-equalizing tubes may be needed.
§ Joint laxity, hip dislocation, or club foot may be seen.
‖ Irritability, hypotonia, and tantrums may begin to be seen.
¶ Seizures may occur in this age group.
# Assess for atypical seizures if any symptoms exist or if intellectual function decreases.
** Infants with fragile X syndrome are often described as stiff and irritable and may feed poorly.
†† Violent outbursts may appear in this age group.
‡‡ Review cytogenetic findings and discuss risks within the family.
§§ Review risk to offspring of affected individual.
‖‖ Family support and issues of what to tell others are important at the time of diagnosis, regardless of the child's age.
¶¶ Address sexual issues.
Ask parents about violent outbursts.
*** Review the preschool program with regard to special educational needs and future placement.
††† Discuss the need for planning for vocational training.

lings and relatives at risk should be provided using DNA-based molecular methods.[11-13] Information that must be related to families includes the features of X-linked inheritance, the predominance of affected males, and the presence of learning impairments and psychological problems in affected individuals. The need to distinguish the premutation from the full mutation sets apart the fragile X mutation from other known X-linked mutations and makes genetic counseling considerably more complex in affected males. In addition, current knowledge suggests that mothers of affected males are carriers of the premutation or the full mutation. The use of up-to-date molecular analysis is critical for accurate risk assessment for these families. Assessment of the number of repeats and the methylation status of the *FMR1* gene must be made. Consultation with a clinical geneticist may be advisable.[14] Prenatal diagnosis is feasible using the same molecular tools used in postnatal diagnosis.[15]

ROUTINE EXAMINATIONS

Several areas should be checked particularly at each visit because of their increased frequency in Fragile X syndrome.

1. Check for strabismus at 6 to 12 months.
2. Check for mitral valve prolapse.[17]
   - Obtain an echocardiogram if a murmur or click is present.
   - Antibiotic prophylaxis can be considered if mitral valve prolapse is identified because of the evidence that connective tissue is not normal in fragile X syndrome.[16,17] The advisability of antibiotic prophylaxis may be controversial unless there is clear evidence of mitral valve regurgitation. Consider consultation with a pediatric cardiologist.
3. Review the personal support available, the emotional status of the parents, and interfamily relationships.
4. At the time the diagnosis is made, review the family history and recommend genetic counseling for family members at risk.
5. Examine the patient for recurrent serous otitis; recommend audiologic examination as indicated.

THE PRENATAL VISIT

Pediatricians may be called on to counsel a family in which a fetus has a genetic disorder. In some settings, the pediatrician may be the primary resource for counseling. At other times, counseling may already have been provided for the family by a clinical geneticist and/or obstetrician. Because of a previous relationship with the family, however, the

pediatrician may be called on to review this information and to assist in the decision-making process. As appropriate, the pediatrician should cover the following topics with the family:

1. Review and demonstrate the laboratory or imaging studies leading to the diagnosis.
2. Explain the mechanism for occurrence of the disease in the fetus and the potential recurrence risk for the family.
3. Review the prognosis and manifestations, including any variability.
4. Review the currently available treatments and interventions. This discussion needs to include the efficacy, potential complications, and/or side effects, costs, or other burdens of these treatments.
5. Explore the options available to the family for treatment and rearing of the child using a nondirective approach. In cases of early prenatal diagnosis, this may include discussion of pregnancy continuation or termination, rearing the child at home, foster care placement, or adoption.

When appropriate, referral to a clinical geneticist should be considered for a more extended discussion of recurrence rates, future reproductive options, and evaluation of risks to other family members.

HEALTH SUPERVISION FROM BIRTH TO 1 MONTH: NEWBORNS

Examination

1. Confirm the diagnosis and review the molecular testing results. In this age group, this diagnosis will probably only have been made when there is a confirmed family history.
2. Review the phenotype and specific findings in the child. Note that these findings are not usually appreciated in the infant.

Anticipatory Guidance

1. Review the support groups and services available to the child and family.
   - Discuss referral for early intervention services.
   - Supply books, pamphlets, and the address and telephone number of the National Fragile X Foundation (1441 York St, Denver, CO 80206; [303] 333–6155 or [800] 688–8765).
2. Discuss individual resources for support, such as family, clergy, and friends.
3. Discuss how and what to tell family members and friends.
4. Review the prenatal diagnosis and recurrence risks for subsequent pregnancies.
5. Assess the family history regarding evaluation of family members at risk.

HEALTH SUPERVISION FROM 1 MONTH TO 1 YEAR: INFANCY

Examination

Early growth and development may be normal.

1. Observe the infant for hypotonia, irritability, tantrums, and seizures at age-appropriate times; recommend early intervention programs that give special attention to these problems.

Anticipatory Guidance

1. Review the availability and use of early intervention programs.

HEALTH SUPERVISION FROM 1 TO 5 YEARS: EARLY CHILDHOOD

Examination

1. Perform an ophthalmologic evaluation using appropriate subjective and objective criteria to check for:
   - Strabismus (seen in 40% of patients);
   - Myopia (commonly observed);
   - Ptosis (occasionally seen); and
   - Nystagmus.
2. At 3 to 5 years, check the child for the following orthopedic problems:
   - Flat feet, scoliosis, and loose joints. Flat feet need to be treated with orthotics only if a gait disturbance exists or the uneven wearing of shoes is severe.
3. Examine the child for inguinal hernias at 1 to 3 years.
4. Assess the child's history for seizures or staring episodes and obtain an electroencephalogram, if appropriate.
5. Assess motor and language development at 3 to 5 years.

Anticipatory Guidance

1. Review the child's preschool program.
   - Review development and school placement and discuss the role of special education needs within a mainstream program, when feasible.
   - Provide speech and language therapy, occupational therapy, and physical therapy as needed.
2. Consider formal developmental evaluation, and discuss the role of behavioral intervention.
   - Check for hyperactive behavior, head banging, and hand biting for possible therapeutic intervention.
3. Review the future reproductive plans of the parents, including recurrence risk and prenatal diagnosis.

HEALTH SUPERVISION FROM 5 TO 13 YEARS: LATE CHILDHOOD

Examination

1. Macro-orchidism may be noted at this age. Reassure parents that this has no relation to sexual function, nor is it a sign of precocious puberty.

Anticipatory Guidance

1. Assess the effectiveness of behavioral intervention.
2. Discuss how parents and siblings deal with behavioral problems.
3. Review the child's development and appropriateness of school placement and the following educational techniques:

- Visual presentation of information;
- Small classroom sizes;
- Individualized attention; and
- Speech, language, and occupational therapy.

HEALTH SUPERVISION FROM 13 TO 21 YEARS OR OLDER: ADOLESCENCE TO EARLY ADULTHOOD

Examination

Hyperactivity may decrease, but attention problems and shyness persist.

1. Assess the adolescent for seizures, especially atypical seizures, particularly if intellectual performance is decreasing.
2. Macro-orchidism may be noted at this age. Reassure parents that this has no relation to sexual function, nor is it a sign of precocious puberty.

Anticipatory Guidance

1. Discuss psychosexual development, physical sexual development, and fertility in boys and girls.
   - Discuss the need for and degree of supervision.
   - Discuss the need for birth control.
2. Review behavioral concerns such as violent outbursts. Aggression or violent outbursts are common in boys and may respond to behavioral or pharmacologic measures.
3. Review genetic mechanisms and discuss the risk to offspring of the affected individual.
4. Assess the need for psychological intervention.
5. Discuss the availability of and need for vocational training and group home placement, if appropriate.
6. Discuss group homes and workshop settings.
7. Facilitate the transition to adult medical care as appropriate or desired.

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