Fragile X Syndrome

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Conclusion

The patient was treated with azithromycin, viscous lidocaine mouthwashes, and intravenous morphine and ketorolac tromethamine. Because of severe pain on swallowing, she was given nasogastric feedings for the first 3 days of hospitalization. She also received a 3-day course of intravenous dexamethasone, followed by a 3-day course of oral prednisone for possible developing pharyngeal and esophageal ulcerations. At the recommendation of an ophthalmologist, her eyes were treated with artificial tears and erythromycin ophthalmic ointment. She responded well to treatment and was discharged from the hospital on hospital day 5.

Even though the patient's SJS was due to *M pneumoniae* infection, the possibility of amoxicillin/clavulanate causing her SJS cannot be excluded.

Suggested Reading

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In Brief

Fragile X Syndrome

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Author Disclosure

Dr Phalen did not disclose any financial relationships relevant to this article.

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Fragile X syndrome (FXS) is the most common inherited cause of mental retardation, with a pattern of transmission that is not typical of X-linked disorders. Women who carry the fragile X chromosome have a surprisingly high risk of expressing some feature of the syndrome, and there are men who have the aberrant gene and are normal clinically. The fragile site at the distal end of the long arm of the X chromosome at position Xq27.3 was discovered in 1969, and the gene responsible for FXS—the fragile X mental retardation-1 (*FMR1*) gene—was isolated in 1991.

The normal *FMR1* gene contains a segment that has 5 to 50 repeated CGG triplets. With the full mutation, there are more than 200 repeats. Men who have a gene that has an intermediate number of CGG repeats (50 to 200) are said to carry a "premutation"; they typically are normal, although they may have mild cognitive impairment. As the number of CGG repeats increases, more cytosine residues are methylated, and the gene becomes inactivated. The failure to make the *FMR1* protein (FMRP) results in the phenotypic expression of FXS.

The mothers of men who have FXS have either the premutation or the full mutation. For women who have a premutation, there is a risk that the number of CGG repeats will increase during either meiosis or early mitosis. If the chromosome is being passed to a daughter, she will be a carrier and have a full mutation; if the chromosome is passed to a son, he will have FXS. Females who have the full mutation are at risk for cognitive impairment.

Whether a man carries a premutation or full mutation, the X chromosomes of his sperm carry only the premutation, and the number of CGG repeats tends to be stable. Thus, men who have FXS pass a premutation to their daughters, and they pass a Y chromosome to their sons, who are unaffected.

The incidence of FXS among boys born to daughters of carrier males is higher than among the brothers of these men. This epidemiologic phenomenon, called the Sherman paradox, is an example of genetic anticipation. Granddaughters are more likely to have affected sons than are their carrier grandmothers. The risk for phenotypic FXS increases with the number of CGG repeats in the mutated gene; on aver-

age, granddaughters have more CGG copies than do their grandmothers.

Epidemiologic data suggest a premutation carrier frequency of 1:100 to 260 females and 1:250 to 800 males in the general population. The full mutation affects about 1:3,600 males and 1:6,000 females. More than 50% of people who have the full mutation are undiagnosed. Approximately 3% of individuals who have previously undiagnosed mental retardation have FXS. The syndrome does not affect lifespan and occurs in all races.

Patients who have FXS have a unique cognitive, behavioral, and physical phenotype. Because of random X inactivation, women generally have milder findings than do men. Early development may appear normal or only slightly slow, but after the first postnatal year, delays become more apparent. As many as 80% of males and 30% of females who have FXS have mental retardation; less severely affected people typically have learning disabilities. Particular weaknesses include poor higher-level thinking, abstract reasoning, complex problem-solving, expressive language, and social skills. Relative strengths involve visual matching and perceptual skills, long-term concrete and emotional memory, verbal comprehension, and self-care. One third of men experience a decline in intelligence quotient after puberty, reflecting their failure to develop abstract reasoning skills rather than an overt loss of intellect. Speech tends to be perseverative, with echolalia and poor intelligibility. Nearly all males and about 50% of females have attention-deficit/hyperactivity disorder (ADHD). Sleep disturbances and feeding difficulties are common, as are mood and anxiety problems among carriers who have a premutation. As many as 90% of affected people exhibit autisticlike behaviors, such as repetitive chewing, hand flapping, poor eye contact, shyness, and intolerance of changes or transitions. Perhaps about 33% of patients meet the full criteria for autism disorder.

Physical findings may be nonspecific, subtle, or not at all apparent until after puberty. Features frequently described as part of the syndrome include a long, thin face with large protuberant ears; prominent forehead, jaw, and nasal bridge; high-arched or cleft palate; strabismus; and joint laxity, dislocated hips, and club feet. Complications may include seizures, scoliosis, and mitral valve prolapse. Macro-orchidism is virtually universal among males, but may not appear until adulthood. Women who carry the premutation are at increased risk for ovarian failure.

Molecular genetic testing is the gold standard for diagnosis. Southern blot and polymerase chain reaction tests both determine the number of CGG repeats. Only the Southern blot test determines methylation status, but it gives a less accurate estimate of the number of CGG repeats if a premutation exists. Patients who have undiagnosed mental retardation, global developmental delay, or autism are candidates for testing. Evaluations by occupational and physical therapists and speech-language pathologists help identify strengths and weaknesses, allowing for targeted therapy. Hearing loss should be ruled out. A tailored educational plan can improve learning, and a child psychologist or behavioral specialist can help manage behavioral problems.

The use of medications must be individualized and monitored closely. Stimulant agents are helpful for ADHD, as are selective serotonin reuptake inhibitors for anxiety disorder. One area of research involves drugs that target glutamate receptors; potentially they can enhance memory and have a low risk for toxicity. Protein replacement and gene therapy also are under investigation.

The pediatrician is the key to coordinating care for the child who has FXS. In 1996, the American Academy of Pediatrics published guidelines that describe FXS fully and provide recommendations for health supervision, anticipatory guidance, and genetic counseling.

Dr Phalen wrote this In Brief while a fellow at The Child Development Unit, The Children's Hospital, Denver, Colo. The views expressed in this In Brief are those of the author and do not reflect the official policy or position of the USAF, Department of Defense, or the United States government.

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