Fragile X Syndrome and Attention-Deficit/Hyperactivity Disorder Symptoms

Presenter: Swapna Deshpande, M.D.¹
Discussant: Barbara J. Coffey, M.D. M.S.²

Chief Complaint and Presenting Problem

H. is a 5-YEAR-OLD Caucasian boy who carries a diagnosis of fragile X syndrome (FXS), mosaic type, pervasive developmental disorder not otherwise specified (PDD-NOS), and attention-deficit/hyperactivity disorder (ADHD). H. was referred for medication consultation regarding his ADHD symptoms to the child and adolescent psychiatry outpatient clinic at a university center.

History of Present Illness

H.'s parents initially became concerned when H. was 18 months old regarding delays in his development in several areas. Specifically, H. did not communicate with his parents or other children his age, and did not make eye contact. At the time of the referral for medication consultation, H.'s parents reported that he only said a few words and used gestures to communicate. He also appeared to understand only part of what was said to him. His speech was unusual, in that he repeated what was said to him. In addition, H. exhibited repetitive behaviors, which included spinning, watching a revolving fan, opening and closing doors, and flapping his hands.

At time of consultation, H.'s problems with frustration tolerance and attentional difficulties were his parents' main concerns. H. reportedly became frustrated easily and threw things when he was upset. His parents were able to distract him about half of the time to prevent prolonged temper tantrums. Limit-setting techniques to address his behavioral difficulties included taking away soda, juice, candy, and activities he enjoyed, and time-outs, which resulted in at least some moderate improvements.

In addition, parents report that H. had a difficult time sustaining attention. He was unable to follow through on simple commands and became distracted easily. H. often had a hard time listening, even when he was asked to do things appropriate to his developmental and cognitive level. Mother described him as being "everywhere all the time," and reported that H. could not sit still and always wanted to touch everything. He could not sit through his class in school, and was reported to be frequently "on the go." He was also reported to frequently shout loudly without any apparent reason.

H.'s mood was reportedly generally good, and he was not aggressive toward others; however, he occasionally banged his head against the wall when upset. Parents reported that H. often seemed very anxious, and had recently developed some new fears, such as a fear of trees, which was reported to come and go. H. also was reported to have difficulty separating from his parents.

Past Psychiatric History

H. was diagnosed with PDD-NOS and ADHD by his primary care physician at the age of two years. H. had not previously been evaluated by a child and adolescent psychiatrist at time of referral.

Developmental History

Mother was 24 at the time of H.'s birth. The pregnancy was complicated by oligohydramnios, observed by ultrasound at 18 weeks, but mother's physician reportedly felt no medical intervention was needed. There were no other medical problems during the pregnancy. Mother experienced premature rupture of membranes and preterm labor at 35 weeks, and H. was born via vaginal delivery. Birth weight was 6 lbs, 6 oz., and Apgar scores were 5 and 7. H. was transferred to the neonatal intensive care unit for 7 days and treated with oxygen for the first 3–4 days.

H. went home from the hospital with his mother, and was cared for by mother and maternal grandparents, as father worked full-time. H. was reported to be very irritable and unable to feed well, and was placed on formula. H. was reported to be hypotonic and had significant delays in all his motor milestones. H. walked at 16 months and babbled late at age 1 year. Toilet training was also reportedly delayed. Mother reports that as an infant, H. did not like to be held and did not show good eye contact.

Educational History

H. began day care at about age 1 year. H. underwent early intervention evaluation at 18 months and was referred for speech therapy for speech and language delays, and occupational therapy for fine motor delays. He also received applied behavioral analysis (ABA) therapy for autism during prekindergarten, with which he had continued through kindergarten at the time of referral.

Social History

H. reportedly had no age-appropriate peer relationships. H. would initiate exchanges of toys with parents but not with unfamiliar people and seldom sought others spontaneously. Parents report that he had only recently begun some pretend play, such as blowing the candles on a birthday cake. He would reportedly say "Look at him." Most of his play was described as repetitive; for example, he would empty toys from one basket to another numerous times.

¹Children's Hospital, Department of Psychiatry and Behavioral Services, University of Oklahoma Health Sciences Center, Oklahoma City.

²New York University Child Study Center, New York, N.Y. and Nathan S. Kline Institute for Psychiatric Research, Orangeburg, N.Y.

Parents are married and have support from extended family. Mother works in health care, and father in an administrative managerial position. H. has one younger sister who is an infant.

Family History

A maternal cousin was reportedly diagnosed with ADHD. Mother was tested and found to be in the premutation range with 83 and 30 repeats of CGG for FXS. Maternal aunt, age 31, has a reading disorder but has never been tested for FXS.

There is no other known family history of tremor, ataxia or other psychiatric or neurological disorders.

Medical History

H's. diagnosis of FXS with repeat mosaicism was confirmed at age 2 years by a pediatric neurologist and genetic testing. H. had CGG 645 repeats and another series of less than 100 repeats. The only other significant medical problem was myringotomy for otitis media twice when H. was age 4 years.

H has reportedly had normal nutrition and physical growth and development. He has always been between 30th to 50th percentile for height and weight.

There are no reported abnormalities of sleep.

H. is allergic to Zithromax, which results in hives.

Medication History

H. was treated with dextmethylphenidate at unknown dosage, which was reported to cause marked loss of appetite and insomnia. H. was then treated with beaded-release methylphenidate up to 20 mg, which resulted in worsening anxiety. He had also been treated with long-acting guanfacine, but significant sedation led to discontinuation. H also was treated with amphetamine 2.5 mg and 5 mg doses; he did not tolerate either dose, becoming more anxious and tearful. Although the lower dose was better tolerated, he reportedly had no reduction in hyperactivity with either dose.

H.'s medication at the time of consultation was clonidine 0.025 mg at lunch and 0.025 mg at bedtime. Parents report at least a partial response with regard to ADHD symptoms and improvement of initial insomnia.

Mental Status Examination

H. was an alert, healthy 5-year old who displayed limited eye contact. His ears were slightly large for his face. He walked on his toes and flapped his hands intermittently. He was very active and constantly touched things. His affect was playful throughout the entire interview. His attention span seemed very short, and he had poor concentration. He was very distracted and enjoyed repetitive play of switching the light on and off. H.'s speech was mostly intelligible. He did not answer questions, but repeated what he heard. He used a few phrases like "Pour it out" and "Go to bed" idiosyncratically. H.'s play included pretending to make popcorn and dinner. He put toys in his mouth. His thought processes and thought content were hard to assess. He thought of the office as the "doctor's house," which indicated some understanding of his orientation to place. H.'s estimated intellectual level was below average, and his judgment and insight were poor.

Consultation Recommendations and Treatment Course

Consultation recommendations included continuation of speech and language therapy, occupational therapy, and ABA in school.

Pharmacotherapy recommendation was for a low dose trial of fluoxetine 2.5 mg to address possible anxiety symptoms and repetitive behaviors. Mother reported improvement in mood and anxiety, and H. was able to tolerate the medication well. However, after two months H. developed repetitive tongue protrusions and the fluoxetine was discontinued. The movements resolved 2 weeks after discontinuation of fluoxetine.

Brief Formulation

In summary, H. is a 5-year-old Caucasian boy with history of FXS with mosaicism, ADHD, and autistic disorder. Genetic risk for fragile X was notable for mother's history of genetic premutation range. Maternal oligohydramnios during pregnancy and respiratory difficulties at birth for which H. needed oxygen might also have contributed to his developmental problems. Pervasive deficits in social communication, repetitive behaviors, and age-appropriate peer relationships were consistent with autistic disorder, and deficits in attentional functioning, hyperactivity and impulsivity were consistent with ADHD symptoms. Psychosocial factors center on H.'s many special needs, which place a tremendous burden on all his caregivers, including parents as well as extended family. Additionally, the local community has limited resources for children with autism and thus increases the burden on the parents.

H. has some strengths to be taken into account, including some capacity for social reciprocity as a result of intervention, development of verbal language, and a family who are able to advocate for him.

Multi-Axial Diagnoses

Axis I:	Autistic disorder (ADHD, combined type)
Axis II:	Mental retardation (IQ unknown)
Axis III:	FXS mosaic type
Axis IV:	Limited resources in the community
Axis V:	Current Global Assessment of Function: 45

Discussion

Several aspects of this interesting case merit discussion, including the unique phenotype of ADHD and autism in FXS. The major factor that determines the presence or absence of FXS is the number of CGG repeats in the FMR1 (fragile X mental retardation) gene on the X chromosome. Typically, if the number of repeats is in excess of 200, it triggers the methylation of the CpG island, a regulatory region for the FMR1 gene. As a result, the production of FMRP (fragile X mental retardation protein) is shut off and the absence of FMRP results in FXS (National Fragile X Foundation website, 2011).

Most humans are in the stable category for the FMR1 gene. The most common number of repeats is 30. They do not have FXS, and they almost always pass on a stable version to their children. Individuals who have from about 45 to about 55 CGG repeats are in the gray zone. They do not have FXS; however, while they usually pass on a stable version to their children, they are somewhat more likely than those in the stable category to have children with an increased number of CGG repeats.

People with about 55 to about 200 are in the premutation range. They generally have few or no symptoms of FXS. However, recent studies have shown that some have subtle intellectual, behavioral, or physical symptoms (National Fragile X Foundation website, 2011).

There has been some controversy about the psychological phenotype of premutation and full mutation mothers (Keysor, 2002). Evidence suggests that mothers in the premutation range are more likely to be anxious (Tsiouris, 2004). It would be interesting and potentially helpful to explore anxiety symptoms in mother, since evaluation and treatment could lead to reduction of symptoms, lessening of the caregiver burden, and potential improvement in quality of time H. spends with his mother.

Around one in three children with FXS have autistic disorder. It has been suggested that FXS is associated with unique features that interfere with social reciprocity, but arise from different core deficits. There may be a unique pattern of hyperarousal and social anxiety that leads to gaze aversion, but children with FXS might still have the desire to communicate socially (Cornish, Sudhalter, & Turk, 2004). With this in mind, it was felt that H. would benefit from a selective serotonin reuptake inhibitor (SSRI), given the evidence supporting its use in this population, and his significant anxiety (Berry-Kravis & Potanos, 2004; Jin, 2003). However, unfortunately it appears that he was unable to tolerate even a low dose. Re-challenge might be considered with another SSRI in the future.

ADHD symptoms significantly impaired H.'s ability to function in the school setting. However, the DSM-IV (APA, 1994) does not allow a diagnosis of ADHD in PDD if the symptoms occur exclusively during the course of the PDD. Symptoms of overactivity and inattention are frequent in autistic disorder, and H. was no exception. ADHD in children with FXS is reported to be characterized by more inattentiveness, restlessness, fidgetiness, and impulsivity, suggestive of the ADHD inattentive sub-type, compared to ADHD in the normal population; these features do not necessarily improve with age (Turk, 1998). FXS's signature is strength in sustained attention, but poor capacity to switch between tasks and weaker inhibitory control (Cornish, et al., 2004). There is evidence that in FXS, ADHD symptoms do respond to stimulants (Berry-Kravis & Potanos, 2004; Tsiouris, 2004). Unfortunately, H. responded poorly to both methylphenidate and amphetamine preparations, becoming more irritable and anxious. However, H. responded at least partially to clonidine, in terms of reduction of some hyperactivity and impulsivity, and improved sleep.

Given H.'s history of intermittent head banging when upset, it was thought that he might benefit from a trial of risperidone, which has been approved for self-injurious and aggressive behaviors in autistic children. Since H.'s self-injurious behavior was not severe at the time of presentation, no specific medication recommendations were made at consultation. The decision to use an atypical antipsychotic in children with autism spectrum disorders requires careful discussion with parents, weighing benefits and risks, specifically regarding weight gain, diabetes and metabolic syndrome. Extrapyramidal adverse effects are less common than with the first-generation antipsychotics but also need to be discussed. Alternatively, there is some evidence that beta-adrenergic antagonists might reduce hyperarousal and aggressive or self-injurious behaviors either alone or in combination with antipsychotics, and thus offer another option for H. (Tsiouris, 2004).

There is evidence supporting the use of nonpharmacological interventions for children with autistic spectrum disorder. H. might also benefit from a system-based approach that incorporates the elements of evaluation of family contexts, its strengths and weaknesses and individual psychological functioning of the parents (Head & Abbeduto, 2007).

To summarize, there are no specific treatments that have been shown to be effective for FXS. Medications can often reduce some target symptoms associated with autistic spectrum disorder,

such as irritability, hyperarousal, impulsivity and attentional dysfunction (Berry-Kravis & Potanos, 2004). ADHD-like symptoms in autistic spectrum disorder may have a very different etiology from those in ADHD, but some of these symptoms may still respond to medications that reduce similar symptoms in ADHD. Hence it is important to evaluate target symptoms and treat them carefully, weighing the risks and benefits of medications (Tsiouris, 2004).

In the future, new medications targeting molecules implicated in the modulation of anxiety, fear, and fear response may be useful for treating social anxiety symptoms and hyperarousal observed in individuals with FXS. Two agents that have shown some promising results are mGluR5 antagonist and AMPA receptor modulator CX516. The antiepileptic 2-methyl-6-phenylethynyl- pyridine (MPEP), an mGluR5 antagonist, has been suggested as a potential treatment for prevention of neuropsychiatric symptoms of FXS, since silencing of the FMR1 gene leads to upregulation of this gene. A preliminary open label study with fenobam, an mGluR5 antagonist, with 12 adults with FXS reported no significant adverse effects with a single dose. Benefits reported included improved eye contact, improved interaction, less perseveration, and "calmed behavior" (Berry-Kravis, 2009). An AMPA receptor modulator is another potential candidate; however, one double-blind, placebo-controlled clinical trial with 49 subjects with FXS failed to show any significant benefit.

More research is needed, particularly with regard to novel agents, to evaluate viable psychopharmacological options for treatment of FXS symptoms.

Disclosures

Dr. Deshpande has no conflicts of interest or financial ties to disclose. Dr. Coffey has received research support from Boehringer Ingelheim, Bristol Myers Squibb, Lilly Pharmaceutical, NIMH, NINDS, Otsuka, Shire, and the Tourette Syndrome Association.

Acknowledgments

We would like to thank James Allen, M.D. for help and guidance in preparation of the manuscript. We would like to thank Stephanie Samar and Resham Gellatly for their assistance in review and preparation of the manuscript.

References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). Washington, DC: American Psychiatric Association; 1994.
- Berry-Kravis E: A pilot open label, single dose trial of fenobam in adults with fragile X syndrome. *J Med Genet* 46:266–271, 2009.
- Berry-Kravis E, Potanos K: Psychopharmacology in fragile X syndrome—present and future. *Ment Retard Dev Disabil Res Rev* 10:42–48, 2004.
- Cornish K, Sudhalter V, Turk J: Attention and language in fragile X. *Ment Retard Dev Disabil Res Rev* 10:11–16, 2004.
- Crawford DC, Acuna JM, Sherman SL: FMR1 and the fragile X syndrome: Human genome epidemiology review. *Genet Med* 3: 359–371, 2001.
- Garber KB, Visootsak J, Warren ST: Fragile X syndrome. *Eur J Human Genet* 16:666–672, 2008.
- Head LS, Abbeduto L: Recognizing the role of parents in developmental outcomes: A systems approach to evaluating the child with developmental disabilities. *Ment Retard Dev Disabil Res Rev* 13: 293–301, 2007.

- Jin P, Warren ST: New insights into fragile X syndrome: From molecules to neurobehaviors. *Trends Biochem Sci* 28:52-158, 2003.
- Keysor CS, Mazzocco MMM: A developmental approach to understanding Fragile X syndrome in females. *Microscopy Res Technique* 57:179-186, 2002.
- Miyashiro KY, Mitchener-Beckel A, Purk TP, Becker KG, Barret T, Liu L, Carbonetto S, Weiler IJ, Greenough W, Eberwine J: RNA cargoes associating with FMRP reveal deficits in cellular functioning in FMR1 null mice. *Neuron* 37:417-431, 2003.
- Saul RA, Tarleton JC: FMR1-related disorders 1. *GeneReviews at GeneTests: Medical Genetics Information Resource*, 2008.
- Tsiouris JA, Brown WT: Neuropsychiatric symptoms of fragile X syndrome: pathophysiology and pharmacotherapy. *CNS Drugs* 18: 687-703, 2004.
- Turk, J: Fragile X syndrome and attentional deficits. *J Appl Res Intellectual Disabilities* 11:175-191, 1998.
- Verkerk AJ, Pieretti M, Sutcliffe JS, Fu YH, Kuhl DP, Pizzuti A, Reiner O, Richards S, Victoria MF, Zhang FP: Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell* 65:905-914, 1991.

Address correspondence to:

Barbara J. Coffey, M.D., M.S.

NYU Child Study Center

577 1st Ave.

New York, NY 10016

E-mail: Barbara.coffey@nyumc.org