

Fragile X Syndrome and Selective Mutism

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This is the first report that details an association between fragile X syndrome (FXS) and selective mutism (SM). This 12-year-old girl with heterozygous full mutation at *FMR1* has a long history of social anxiety and shyness in addition to SM. Her sister also has the full mutation and a history of SM that resolved in adolescence. A beneficial response to fluoxetine and psychotherapy is described. The *FMR1* mutation appears to be the first gene mutation associated with SM and further studies are recommended to assess what percentage of patients with SM have the *FMR1* mutation. Am. J. Med. Genet. 83:313–317, 1999.

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INTRODUCTION

Previous reports have emphasized the association between selective mutism (SM) and abuse or traumatic events [Hayden, 1980; Kolvin and Fundudis, 1981; MacGregor et al., 1994] and passive aggressive or oppositional behavior [Hayden, 1980; Kolvin and Fundudis, 1981]. Recent studies have found a significant association between selective mutism and anxiety symptoms including shyness, panic episodes, social phobia, avoidant disorder, and most importantly, social anxiety [Black and Uhde, 1992; Black and Uhde, 1995; Black, 1994; Crumley, 1990; Dummit et al., 1997]. In a study of 30 children with SM, 97% met diagnostic criteria for social phobia, avoidant disorder, or both, whereas only 13% reported a history of physical or sexual abuse and only 10% had a diagnosis of oppositional defiant disorder, and the oppositional behaviors were not a primary concern for the families [Black and Uhde, 1995]. Simi-

lar results were reported by Dummit et al. [1997] in a study of 50 children with SM where all 50 met criteria for social phobia or avoidant disorder and 48% had additional anxiety disorders. In addition, Black and Uhde [1995] also found a significant family history of anxiety problems, with first-degree relatives demonstrating social phobia in 70% of families and SM in 37% of families. In 22% of the families, the parent was selectively mute. Similar rates of family involvement have also been reported by others [Brown and Lloyd, 1975; Browne et al., 1963]. The disorder is somewhat higher in females than in males [Dummit et al., 1997; Kolvin and Fundudis, 1981].

Klin and Volkmar [1993] reported two cases of SM associated with mental retardation and reviewed three other studies that reported cognitive deficits in association with SM [Kolvin and Fundudis, 1981; Kupietz and Schwartz, 1982; Reed, 1963]. None of these patients were tested for fragile X syndrome (FXS). Several authors report the association of speech and language problems and SM [Gidden et al., 1997; Kolvin and Fundudis, 1981; Wilkens, 1985; Wright et al., 1985].

Dow et al. [1995] describe guidelines for the assessment and treatment of SM and they include detailed cognitive, language, academic, audiological, social, and psychiatric assessments in addition to studies of the family history. However, in this description of the current guidelines for assessment there is no mention of testing for FXS or other laboratory studies. Since we have occasionally seen a female with FXS and SM [Hagerman, 1996a], we are reporting a detailed case study to emphasize the need for further research regarding this association.

FXS is the most common inherited form of mental retardation known; however, it also causes a spectrum of learning and attentional problems without mental retardation [Hagerman, 1996]. Shyness and social anxiety are core manifestations in males and females with FXS [Hagerman, 1996b; Lachiewicz, 1995; Sobesky et al., 1995]. Freund et al. [1993] studied 17 females with FXS and found 65% with avoidant disorder in childhood or avoidant personality disorder and 47% with mood disorder that was significantly different from age- and IQ-matched controls. Approximately 50 to 70% of females with a full mutation (greater than 230 CGG repeats) in the *FMR1* gene have cognitive abilities in the borderline or mentally retarded range

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[de Vries et al., 1996; Hagerman et al., 1992]. Those females with the full mutation and an IQ greater than 70 usually have learning difficulties including executive function deficits, math problems, and language difficulties [Bennetto and Pennington, 1996; Lachiewicz, 1995; Mazzocco and Holden, 1996; Sobesky et al., 1996].

Shyness and social anxiety in addition to prominent ears are helpful characteristics for the clinician in distinguishing sisters who carry the full mutation from sisters who do not [Hagerman et al., 1992]. Because of the strong association of shyness and social anxiety and FXS, in addition to the familial nature of the disorder, it is not surprising to see the concurrence of FXS and SM in girls and their relatives as reported here.

CLINICAL HISTORY

Karen is a now 12-year-old young lady in the sixth grade in middle school. She was diagnosed with FXS at the age of 8 years after DNA testing demonstrated a full mutation with a CGG repeat expansion to 497, which was fully methylated. Her gestation was normal. Her mother did not take medication nor alcohol during the pregnancy and she was born at term with a birth weight of 7 lb. 14 oz. She walked at 11 months, saying words in the first year, but she was mildly delayed in speaking in phrases until after age 3 years. She was able to talk well with her sister and her mother, but she has always had difficulties in speaking to her father. In general, she answers his questions but does not speak to him spontaneously. She would also never initiate conversation with individuals outside of the family and she is described as "painfully shy" with others.

In her early schooling she would simply answer teachers' questions with as short a response as possible and after the fourth grade she has not spoken in sentences at school. Last year, her best friend moved out of town and after this episode she completely stopped talking at school. She does not have a history of abuse or trauma. She is generally anxious about many social situations and she has a history of rare panic attacks, including one episode when she felt she was expected to play the saxophone in the school band. She has received speech and language therapy since the first grade, in addition to learning disability support, particularly for math difficulties, in school.

In addition to her shyness and social anxiety, she has had poor eye contact throughout her childhood, in addition to tactile defensiveness and sensitivity to tags in her clothes. She has never had hyperactivity nor significant attention problems. Tantrums or physical aggression are not problems for her nor is she oppositional. Her past medical history includes a tonsillectomy and adenoidectomy at age 9 years because of multiple streptococcal throat infections. She has never had otitis media infections nor sinusitis. She had one febrile seizure at age 3 years and she has never had a motor tic nor psychotic ideation. She has not yet experienced menarche.

Her sister Lucy is 17 years old and similarly did not speak in school during the fifth and the sixth grades. Her language in school gradually increased after pu-

berty and her SM resolved. She is talkative in school now and has a boyfriend. She has also had a history of significant anxiety, poor eye contact, and the full mutation on fragile X DNA testing. Mother has the pre-mutation and has a history of not talking in school for a period of time, but the details are not well remembered. Mother has two sisters who have boys with FXS. One male cousin has FXS with mental retardation and ADHD, and another male cousin has a mosaic pattern on DNA testing with severe ADHD and aggression but an IQ of 100.

On examination, Karen's height is at the 35th centile for age, weight at the 50th centile for age, and head circumference at the 80th centile. She was shy and mute on examination and she demonstrated poor eye contact. Blood pressure was 115/70 mmHg and heart rate was 80/min. She had a prominent forehead and a mildly long face. Eyes were normal and her ears were mildly prominent. Her palate was narrow and high arched but her jaw was not prominent. Chest and heart were normal and breast development was Tanner stage 2, genitalia development was Tanner stage 1. Her skin was soft and smooth, her finger joints were mildly hyperextensible with metacarpal phalangeal extension to 80°, thumbs were not double jointed, and palmar creases were normal. Her feet were not completely flat and a hallux crease was present on the bottom of her foot. Deep tendon reflexes were 2+ and symmetrical, Babinski reflex was absent, and there was no tremor. Mild visual motor coordination problems were seen in her handwriting and in her picture drawing.

Due to the total lack of verbalization with strangers, Karen's assessment of speech and language was completed using a pointing response and the Peabody Picture Vocabulary Test III (PPVT-III), as well as use of head nods and gestures to indicate responses to questions about her speech habits across typical settings. Her receptive vocabulary was within the average range with a standard score of 90 and a percentile rank of 25. A summary grid [Cline and Baldwin, 1994] of speech habits across settings was completed by having Karen utilize gestures and nods to indicate responses. Karen's SM across different settings and with different people was assessed. She reported that she feels she speaks normally and with normal loudness at home and with her mother and sister but will not initiate speech with her father. More specific language testing had been completed through her school one year ago in a non-standardized manner by having Karen's best friend administer the tests. The results of the testing showed significant receptive and expressive language delays with almost all scores below the 9th percentile. Results of the semantic relations subtest of Clinical Evaluation of Language Fundamentals Revised (CELF-R) were within the average range and the therapist assisting in administering the test felt that the written words accompanying the verbal text were helpful cues for Karen. Articulation, fluency, as well as volume were assessed as being normal when Karen was observed in conversation with her good friend or mother.

Speech/language therapy in school focused on praise for any attempts at whispering or vocalizing. The school speech/language pathologist felt all attempts at

encouraging Karen to vocalize were unsuccessful. We recommended that any demands for speech in anxiety-provoking situations, such as asking her direct questions in front of the class, be stopped. A hierarchical progression toward vocalization using a token-economy system as described in Gidden et al. (1997) was also recommended as part of her overall treatment program.

A psychological evaluation was completed prior to her treatment described below. Karen was socially immature for her age. Karen's mother and her mother's sister (Karen's aunt) participated in the evaluation to help decrease her anxiety. As the evaluation progressed, Karen's anxiety intensified. Although initially able to communicate with the use of nonverbal gestures, by the end of the session, she was unable to communicate nonverbally. Karen completed a checklist regarding how much she worries about things. Karen's self-ratings were inconsistent and were not supported by her mother's report. As Karen's symptoms of anxiety intensified across the evaluation, she became less able to participate actively, even when she seemed to want to do so. She was unable to complete projective drawing tasks, even when the examiner left the room and provided an opportunity for her to complete these with her mother's assistance. Because of Karen's high level of anxiety, the rest of the evaluation was completed by parent interview and a review of the records. A Vineland Adaptive Behavior Scale showed a Communication score of 75 (9 years 0 months), a Daily Living Skills score of 77 (9 years 6 months) and a Socialization score of 66 (6 years 9 months). Her Adaptive Behavior Composite was 67 (8 years 5 months), which corresponds to low to moderately low in comparison with other children her age.

Results of school testing completed during the fifth grade need to be interpreted extremely cautiously. The school psychologist reported that the WISC-III was administered with one of Karen's friends present. Karen whispered her answers to her friend, who then reported them to the psychologist. The results attained include a prorated Verbal IQ of 62 and a prorated PIQ of 86. Karen's symptoms of anxiety are quite general in that there are a variety of circumstances around which Karen becomes anxious. In addition to SM, she meets diagnostic criteria for generalized anxiety disorder and learning disorder, NOS. Karen seemed to have very specific rules governing with whom and under which situations she could talk. Karen's history of SM is clearly long-standing. Karen was referred for individual psychotherapy with a psychologist experienced working with children with learning problems and with children with SM.

Karen's treatment program consisted of a multiprofessional approach coordinated by her developmental and behavioral pediatrician (RH) and her psychologist (HL). Her program included psychotherapy, medication, speech and language therapy, and special education support.

Psychotherapy was provided with a child/family psychologist who integrated behavioral, cognitive, and dynamic aspects of treatment. The psychotherapy included (1) establishment of a trusting relationship with

Karen with emphasis on alternative means of self-expression and expectations for speech reduced or eliminated; (2) clarification and validation of Karen's complex rules regarding where, when, and to whom she can or cannot speak and permission to change those rules gradually if in her best interests; (3) direct, metaphorical, and paradoxical suggestions regarding ways in which Karen can be in control of situations and cope with conflicts; (4) exploration of Karen's inner conflicts, areas of anxiety and fear, and painful experiences; (5) adjunct family therapy to increase expectations of Karen regarding independent functioning, to promote Karen's understanding of how her family's expectations of her are changing, and to enhance Karen's understanding of the extent to which she is reiterating her sister's history and her freedom to chart her own course; and (6) consultation with family and school personnel regarding how to reduce attention and other secondary gain provided to Karen for "silent behavior"; this includes reduction of overt reinforcement for speaking because the preceding "silent behavior" is part of a longer chain of behavior being reinforced and because such reinforcement may provide an explanation for speaking (i.e., external justification) and block internal attributions about wanting to speak.

Fluoxetine was initiated to decrease her anxiety and facilitate speech. She tolerated her initial dose of 10 mg per day without any side effects. Within the first 30 days of her treatment program, which included psychotherapy and counseling, she began verbalizing spontaneously with her father and she increased her verbalizations with family friends and relatives. Nonverbal communication improved at school during her first month on treatment and then school let out for the summer. Her fluoxetine dose was increased to 20 mg/day and she and her family continue in weekly therapy. She and her parents are pleased with an improvement in mood and a decrease in anxiety.

DISCUSSION

This case represents the first detailed description of SM in a girl with FXS. She demonstrates classical SM including anxiety, panic episodes, a good response to fluoxetine and psychotherapy, and a family history of SM in the sister who also has a full mutation and possibly in the mother who only has a premutation. Although Karen has learning disabilities and language deficits caused by FXS she is not mentally retarded. It is the anxiety and social phobia of FXS that appears to predispose her to SM. None of the males in this family have SM and we have not seen SM in association with males and FXS. We have seen six females with FXS and SM, including the two well-documented cases in the family reported here. We have not systematically studied our whole population of females with FXS (approximately 100), although such a study is warranted.

Shyness and social anxiety are pervasive problems in FXS and in males, the poor eye contact and tactile defensiveness are usually associated with other autistic-like behaviors such as flapping and hand biting [Cohen et al., 1989; Hagerman, 1996a]. Such stereotypes also occur in approximately 35% of girls with FXS [Freund

et al., 1993]. Autism, which represents the most severe end of the spectrum of social anxiety and social withdrawal, occurs only occasionally in females with FXS [Bolton et al., 1989; Edwards et al., 1988; Gillberg et al., 1988; Hagerman et al., 1986; Le Couteur et al., 1988]. Screening studies of autistic females have yielded 12.1% [Cohen et al., 1989] and 5% with FXS [Bailey et al., 1993]. Therefore, it is recommended that all females with autism should be screened for FXS. However, such a recommendation has not yet been made for severe anxiety disorders or avoidant disorders, which are strongly associated with FXS in females.

ADHD is seen in approximately 35% of females with FXS [Freund et al., 1993; Hagerman et al., 1992]. The presence of significant impulsivity and hyperactivity is negatively correlated with the severity of shyness and social anxiety in females with the full mutation [Sobesky et al., 1995; Sobesky et al., 1996]. Therefore, ADHD may be somewhat protective from significant social anxiety particularly from a severe form that could lead to SM. The girl reported here did not have ADHD. Most males with FXS have some degree of ADHD and perhaps this is why we have not seen SM in males with FXS.

Black and Uhde [1994] have reported a double-blind, placebo controlled study of fluoxetine in the treatment of 15 patients with SM. They found significant improvements over placebo in parent ratings of mutism change and global change. Dummit et al. [1996] and others [Wright et al., 1995] have also reported on the benefit of fluoxetine in patients with SM. Fluoxetine has been reported to be beneficial in treatment in FXS, particularly for anxiety, depression, and aggression, although no controlled studies have been carried out [Hagerman, 1996a; Hagerman et al., 1994].

We recommend further studies regarding the association of SM and FXS. These studies should include DNA *FMR1* studies in children with SM, particularly if they have language and/or cognitive deficits or a family history of SM, autism, or mental retardation. The diagnosis of FXS is important to make because of the need for genetic counseling in multiple family members since the risk for a carrier to pass on the mutation is 50% [Cronister, 1996]. The diagnosis of FXS can also help to organize treatment and intervention known to be helpful in FXS [Hagerman, 1996a; Scharfenaker et al., 1996; Schopmeyer and Lowe, 1992; Spiridigliozzi et al., 1995]. The *FMR1* mutation appears to be the first gene mutation associated with SM, although many more will no doubt be found in the future.

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