

Autism in Fragile X Females

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We present two women with the fragile X syndrome (Martin-Bell syndrome) and autism. Both are mentally retarded, one mildly and one severely. Cytogenetic studies showed a high percentage of lymphocytes with the fragile X chromosome and inactivation occurring preferentially in the normal X chromosome.

Autism is shown to be a severe behavioral and cognitive manifestation of the fragile X syndrome in females.

Key words: autism, fragile X syndrome, heterozygous female, Martin-Bell syndrome

INTRODUCTION

The association between autism and the fragile X [fra(X)] or Martin-Bell syndrome (MBS) in males was first described by Brown et al [1982a,b]. Further case studies of autistic fra(X) males [Meryash et al, 1982; Levitas et al, 1983; Jørgensen et al, 1984; August and Lockhart, 1984; Gillberg, 1983] have confirmed this association. A large multicenter study of autistic males demonstrated the fra(X) chromosome in 16% (13/83) [Blomquist et al, 1984]. Studies of males with the fra(X) syndrome show autistic-like features including reduced eye contact and unusual hand mannerisms in the majority [Hagerman et al, 1983a; Hagerman et al, 1986].

However, autism in fra(X) females has not been observed before. There are two populations of heterozygous fra(X) females, the clinically affected and the unaffected. The affected woman may have characteristic physical anomalies similar to those in males with the syndrome, including large or prominent ears, highly arched palate, long face, and hyperextensible fingers [Hagerman et al, 1983b]. Approximately 30%

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of heterozygous females are considered mentally impaired with an IQ of < 85 [Sherman et al, 1984]. Fishburn et al [1983] have described educational retardation, including learning disabilities and mild retardation, in up to 56% of obligate carriers. More severe retardation has been reported in females [Brøndum Nielsen et al, 1981; Webb et al, 1982], but this appears to be an occasional finding. Chudley et al [1983] have confirmed an inverse relationship between percent fragility and IQ, in that increased frequency of fragility was associated with a lower IQ. There is also a correlation between inactivation of the fra(X) chromosome and cognitive involvement of the heterozygous female [Knoll et al, 1984; Jacobs et al, 1980; Uchida and Joyce, 1982; Uchida et al, 1983; Paul et al, 1984].

Although the biochemical basis for the cognitive impairment in the fra(X) syndrome is not known, clinicians should be aware of the spectrum of behavioral and cognitive problems that may be present in women with this syndrome. Here we describe two heterozygotes with the fra(X) syndrome who have autism and mild to severe mental retardation.

CLINICAL REPORTS

Patient 1

This 25-year-old mildly retarded woman was found to have the fra(X) after the MBS diagnosis was made in her retarded brother. The pregnancy and birth history were normal. In the first month of life, the patient had difficulties sucking from breast and bottle, so she was fed cereal and learned to drink from a cup in infancy. She was described as an irritable baby and had tantrums as a toddler. She learned to sit at approximately 7 months and was walking between age 16 and 18 months. Speech was more severely delayed. She started speaking in single words between age 4 and 5 years. Parents described her as "in a world of her own" and unable to relate to anyone in her environment.

She was first evaluated at 5 years because she ignored the other children in her kindergarten classroom. She often chewed her clothing and when anxious she would wring or twist her hands. She was described by parents and professionals as withdrawn, resistive, passive, and indifferent. The parents were also concerned about hyperactivity and staring spells. Stanford-Binet IQ was 72, Leiter score 51 and the IQ equivalent score was 107 on the Peabody Picture Vocabulary Test [1981]. Hearing was normal and an ophthalmological exam showed hyperopia. An EEG was abnormal and showed occipital slowing and spike wave foci in the right occipital and right posterior temporal region. Diphenylhydantoin was prescribed, but her behavior, staring spells, and withdrawal did not change.

Autism was suggested by a psychiatrist because of her withdrawal. Subsequent play therapy was only minimally helpful.

Throughout grammar school she was placed in special education programs. She did well in reading and spelling but very poorly in math. Her social withdrawal continued and at 13 years a residential placement was recommended to improve her socialization skills.

Presently at age 25 years she is described as a loner who lacks interest in socializing, and prefers to sit alone and read Agatha Christie novels. She speaks in a high falsetto voice and rarely initiates conversation, although she will answer questions, usually in a single word. She wrings her hands and rocks slowly, particularly when she is anxious.

At diagnosis (age 25 years), she had a height of 155 cm (5th centile), weight of 52 kg (25th centile), and head circumference (OFC) of 54 cm (30th centile). Her face was narrow with large and prominent ears, a highly arched palate, and dental malocclusion. The heart and echocardiogram were normal. She had mild hyperextensibility of fingers and flat feet. Psychological testing demonstrated a Stanford-Binet IQ of 42 and a Peabody Picture Vocabulary Test [1981] IQ of 95. She avoided eye contact with the examiner, never initiated a conversation, slowly rocked her body while staring at the floor, and answered questions with only one or two words, using a high falsetto voice and occasional echolalia. She scored 86 on the Autism Behavior Checklist (ABC) [Krug et al, 1980]. (Scores greater than 67 are in the autistic range.) She also fulfilled the DSM III criteria for Infantile Autism [APA, 1980]. Her brother and sister showed the fra(X) site, but her sister is considered an unaffected heterozygote.

Patient 2

This 38-year old, severely mentally retarded woman was found to have the fra(X) during a cytogenetics survey in an institution for the mentally handicapped. She was the sixth child born to healthy, unrelated parents. She was delivered at 36 weeks after a normal and uncomplicated pregnancy. Her birth weight is unknown and she was described as "underweight" and requiring incubator care for the first 4 weeks of life. She walked at 2 years, but never developed any meaningful speech. She was toilet trained at 9 years. Her parents described her as a "nervous" child; although affectionate, she did not like being touched and never developed meaningful relationships with other children. She would sit for hours on the couch, rocking to-and-fro and moving her head from side to side. She preferred to play with a piece of paper or chain, holding it close to her face and shaking it against her cheek. Although described as a good natured child, she had frequent temper tantrums when teased and would pick up objects close at hand and hurl them at people. At 9 years, she was admitted to a provincial institution for the mentally retarded.

At age 8 years, she did not successfully complete any test items on the Stanford-Binet. During the interview, she sat on the chair rocking, flapping her hands and grimacing. Her social age was 17 months on the Vineland Social Maturity Scale. At 24 years, she had a social age of 4.2 years and scored a mental age of 2 years 3 months on the Stanford-Binet. She completed only visual motor tasks and perseveration was noted in her responses. She was nonverbal and very distractible during the session. On the ABC, she scored 80 and fulfilled all of the DSM III criteria for autism.

Her health has been good apart from an occasional grand mal seizure, which is presently controlled with diphenylhydantoin. A recent EEG was reportedly normal.

Little information is available from the family since both her parents are deceased. Apparently, the mother had ten children and three miscarriages. The patient has three brothers who are mentally retarded, one being fra(X) positive (43/100); the other two have not been studied. She has one sister, who is described as a "slow learner" and four other brothers and one sister who are apparently of normal intelligence. Neither parent completed elementary school and both were considered below average intelligence.

On examination, she was highly anxious and demonstrated marked eye and tactile aversion. Her OFC was 54 cm (25th centile), height was 155 cm (5th centile) and weight 45 kg (10th centile). She had a long face, marked crowding of the teeth,

and a high-arched palate. Her ears were not enlarged. She did not show evidence of joint hyperextensibility and in all other respects, she was normal.

Chromosome Investigations

Peripheral lymphocytes were established in folate and thymidine deficient medium, as described previously [Chudley et al, 1983]. Fra(X) chromosomes were scored after G-banding. Replication patterns were determined using BrdU incorporation followed by acridine orange staining as previously described [Hagemeyer et al, 1976]. A fra(X) was seen in 29/100 metaphases analyzed in Patient 1. An excess number of early replicating fra(X) chromosomes were identified in 25 cells evaluated: 16 early replicating vs 9 late replicating fra(X) chromosomes.

A fra(X) was seen in 45/100 of the metaphases studied in Patient 2. An excess number of early replicating fra(X) positive chromosomes was identified in 25 cells evaluated: 18 early replicating vs 7 late replicating fra(X) chromosomes (combining data for both patients, X^2 , with Yates correction = 5.78; $p = 0.016$). A pericentric inversion of a chromosome 2 was seen in all metaphases giving her the karyotype 46,XX, fra(X) (q27.3), inv(2) (p11q13). We think that this is an incidental and probably benign finding [MacDonald and Cox, 1985; Phelan et al, 1984]. One normal brother and one fra(X) positive brother did not have the inversion. Since other relatives are not available for study, we do not know whether this inversion was inherited or arose *de novo*.

DISCUSSION

The association of the fra(X) syndrome and autism has been well described in males but not in females. These two affected heterozygous fra(X) females fulfill the DSM III criteria for Infantile Autism [APA, 1980]. Both cases demonstrated behavioral and developmental problems beginning in the first year. Difficulties in relating to others were present throughout childhood and adulthood. Patient 2 was nonverbal, but Patient 1 had an unusual speech, including a high falsetto voice and perseverations. Both women were tactiley defensive with eye avoidance and displayed unusual mannerisms such as rocking and hand flapping.

Each patient scored within the autistic range in the ABC [Krug et al, 1980], which was filled out by the primary caretaker. This checklist is a compilation of 57 behavior descriptors commonly associated with autism. A score of 67, or 0.5 standard deviations below the autistic population mean total of 77, has been selected by Krug et al [1980] as a high probability cut off point for the classification of autism. Both patients scored in the 80s which is in the midrange for a population of autistic individuals.

Each woman clearly has the fra(X) syndrome, or MBS, physically, cytogenetically, and cognitively. Most affected women with the fra(X) syndrome have only mild problems including learning disabilities or mild retardation without severe behavioral problems. The two patients described here represent more severe involvement in the female and perhaps represent one end of a behavioral spectrum. In the authors' experience milder difficulties of relating, such as reduced eye contact, shyness, and social withdrawal are seen rather frequently in affected heterozygous fra(X) women. These traits can be helpful diagnostically and we recommend chromosome studies in all autistic or retarded females.

Both women have high fra(X) expression, a finding that has been correlated with mental handicap by some investigators [Chudley et al, 1983; Fishburn et al,

1983], but is considered a familial variation and not highly correlated with IQ by others [Soudek et al, 1984]. Studies on the replication pattern of the fra(X) in carriers show conflicting results [Brøndum-Nielsen et al, 1983; Fryns et al, 1984; Knoll et al, 1984]. For the most part, mentally handicapped carriers have a higher proportion of active fra(X) than inactive fra(X) chromosomes when compared to normally intelligent carriers [Jacobs et al, 1980; Uchida and Joyce, 1982; Uchida et al, 1983; Howell and McDermott, 1982; Knoll et al, 1984; Paul et al, 1984; Tuckerman et al, 1985]. Both carriers in this report showed an excess of active vs inactive fra(X) chromosomes supporting a relationship between mental and/or behavioral abnormalities and replication patterns of the fra(X).

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