Brief Reports

Brief Report: Autistic Behaviors Among Children with Fragile X or Rett Syndrome: Implications for the Classification of Pervasive Developmental Disorder

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INTRODUCTION

Autism is a behavioral disorder characterized by impaired social interaction, impaired communication, and a restricted range of activities and interests that emerge during infancy or early childhood (American Psychiatric Association [APA], 1987, 1994). Although most individuals with autism (75%) have mental retardation, manifestation of the behavioral criteria for autism described in the Diagnostic and Statistical Manual of Mental Disorders (DSM) vary in frequency, type, and severity across individuals with the diagnosis. Some individuals who do not meet the diagnostic criteria for autism exhibit behaviors that fulfill only a subset of these criteria. For example, fragile X syndrome has been associated with autism, yet reports on the prevalence of nonverbal communication deficits and stereotypic behavior in this population vary greatly. In contrast, among children with Rett syndrome the prevalence and specificity of autistic behaviors has been more consistently established.

Although the etiology of autism is currently unknown, there is considerable evidence to suggest genetic involvement. For instance, data from magnetic resonance imaging studies support cerebellar abnormalities in autism, particularly in the vermal regions, and increased ventricular size (Courchesne, Young-Courchesne, Press, Hesselink, & Jernigan, 1988; Gaffney, Kuperman, Tsai, & Minchin, 1988; Gaffney, Tsai, Kuperman, & Minchin, 1987). The notion that genetic factors underlie autistic disorder is supported by the high concordance rate for autism in monozygotic twins (Folstein & Rutter, 1977; Smalley, Asarnow, & Spence, 1988), and the higher prevalence rates of autism, relative to rates in the general population, among first-degree relatives of autistic probands (Folstein & Rutter, 1977). Information regarding autistic behaviors associated with known genetic conditions may contribute toward understanding the biological mechanism involved in autism and may have implications for the classification of pervasive developmental disorders (PDD). In this report, autistic behaviors among males with fragile X syndrome and females with Rett syndrome (RS) are compared to each other and to behaviors among genetically heterogeneous groups of children with neurological impairment, including autism.

The two disorders examined in this study differ in frequency and phenotype. Fragile X syndrome has an incidence of approximately 1:1000 (Sherman, 1991). The gene mutation most commonly associated with fragile X syndrome was identified in 1991 as an expansion of a nucleic acid repeat, cytosine–guanine–guanine (CGG) (Verkerk et al., 1991). Expansion size of this mutation refers to the number of CGG triplet repeats within the gene. Mutations in excess of 200 repeats are usually associated with methylation and with an affected phenotype, and are classified as “full
mutations." In the present study, the individuals in the fragile X group had the full mutation.

The physical phenotype of fragile X syndrome is well documented, but it is variable and sometimes is not apparent in individuals with the disorder, especially young children. This phenotype includes a long face with prominent forehead, large protruding ears, a high arched palate, hyperextensible joints, and, in males, macroorchidism (see Hagerman, 1996, for a review). A specific yet variable psychological phenotype has also been described (see Baumgardner, Green, & Reiss; Mazzocco & Reiss, 1998, for a review). Psychological effects may include learning disability, language disorders, behavioral disturbances, poor adaptive functioning, or mental retardation. Neuroanatomical studies of fragile X indicate specific brain structure anomalies, including anomalies also reported for individuals with autism such as decreased size of the posterior cerebellar vermis (see Abrams & Reiss, 1995, for a review).

Since the association between autism and fragile X was first proposed by Brown et al. (1982), it continues to be a point of controversy. Extreme variability (0–60%) exists across reports of autistic behaviors in individuals with fragile X (Brown et al., 1982; Hagerman et al., 1986; Levitas et al., 1983; Wisniewski et al., 1985). This variability most likely reflects differences in the definitions and criteria of autistic behavior on which research studies have been based. The specificity of autistic-behavior profiles in males with fragile X, as described by Reiss and Freund (1990, 1992), includes social interaction deficits, stereotypies, abnormal communication, and abnormal responses to sensory stimuli; but does not include deficits in attachment to or interaction with caregivers. A similar profile of autistic behaviors has been observed in females with fragile X (Mazzocco, Kates, Baumgardner, Freund, & Reiss, 1997).

Reit syndrome is a rare neurodevelopmental disorder that occurs almost exclusively in females, with an incidence rate of approximately 1:22,000 females (Kozinetz et al., 1993). The genetic etiology of RS is unknown. Evidence that RS, like fragile X, is an X-linked disorder (Comings, 1990) has not been accepted by some researchers (Migeon, Dunn, Thomas, Schmeckpeper, & Naidu, 1995). The lack of a genetic marker for RS leads to diagnostic challenges and reliance on clinical diagnostic criteria. Girls affected with RS apparently have a normal head circumference and a normal course of development through the first 5 months of life. Subsequently, a rapid developmental regression occurs between 5 to 48 months of age, and is characterized by deceleration of head growth, loss of purposeful hand skills, diminished social skills, breathing irregularities (such as hyperventilation or breath holding crises), severely impaired expressive and receptive language development, and autistic behaviors. A characteristic feature of the syndrome is stereotyped activity that resembles hand-wringing or hand-washing. The initial developmental regression is followed by a slower progression of neurological deterioration and subsequent severe to profound mental retardation and progressive gait difficulties.

The incidence of autistic behaviors in RS has long been well established, although the notion that RS represents a qualitative subtype of autism has been suggested more recently (Gillberg, 1987, 1989; Olsson & Rett, 1987). The significant neuroanatomical volumetric abnormalities demonstrated in females with RS (Reiss et al., 1993) include reduced cerebral volume, with variation in degree of reduced gray matter across different cortical regions; reduced cerebellar volume; and reduced volumes in midsagittal areas of the anterior cerebellar vermis (Murakami, Courchesne, Haas, Press, & Young-Courchesne, 1992). Decreased levels of dopamine, norepinephrine, and serotonin have been reported among girls with RS (Zoghbi et al., 1989). Still, the neuropathology of a neuroanatomy-behavior association in RS is currently not understood.

In this study, the incidence of specific behaviors associated with autism were examined among a small group of individuals with fragile X or RS, relative to individuals with neither disorder who had other etiologies of developmental or neurological impairment. The behaviors examined correspond to the diagnostic criteria established in the DSM-III-R (APA, 1987). These behaviors were examined rather than those presented in DSM-IV because interviews for the study began prior to the publication of the DSM-IV.

**METHOD**

**Participants**

The subjects included 14 males with fragile X syndrome, 12 females with RS, and 25 individuals in a comparison group including 14 males and 11 females.
Males Participants. The 14 males with fragile X represent half of the patients diagnosed with fragile X at the Pediatric Clinic of Catania during the subject recruitment phase of this study. Fragile X was initially diagnosed by folate-deficient cytogenetic testing. For 12 of these 14 patients, fragile X was later validated by lymphocyte-derived DNA analysis at the FMR-1 gene via EcoRI + Eag I digest with the StB 12.3 probe (Oberle et al., 1991). Parents of the remaining 14 males with fragile X declined to participate in the study. Their reasons for nonparticipation included distance to the clinic and the time necessary for the completion of an interview by two independent examiners. Individually age-matched (within 1 year) males with mental retardation who did not have fragile X were successfully recruited as members of the comparison group. These males were referred to the Pediatric Clinic of Catania for evaluation of developmental delay, including autism. In view of the fact that the Pediatric Clinic of Catania provides specialty assessment and care (vs. general pediatric care), the comparison group recruited through this clinic was not intended to represent a “normal” control group. This comparison group of non-fragile X males included males with trisomy 18, trisomy 21, muscular dystrophy, leukodystrophy, or seizure disorder. The males within both groups ranged in age from 4 to 21 years.

Female Participants. The 12 females with RS represent 60% of the 20 Rett patients seen at the Pediatric Clinic of Catania who received this diagnosis. Diagnosis of RS was based on clinical criteria as established by Percy, Gillberg, Hagberg, and Witt-Engerstrom (1990). Eleven females with mental retardation who did not have a diagnosis of RS were successfully recruited for the comparison group. The 11 pairs of females were matched on age within 1 year, with the exception of a 21-year-old female with mental retardation in the comparison group who was matched with a 24-year-old female with RS. The females in this comparison group were referred to the Pediatric Clinic of Catania for evaluation of developmental delay. The diagnoses included among these females were metabolic disorder, seizure disorder, Turner syndrome, Weaver syndrome, Leber amaurosis, William syndrome, early history of encephalitis, or myotonic dystrophy. The females in the study ranged in age from 3 years 6 months to 24 years, and 4 to 21 years, for the Rett and comparison groups, respectively. A 12th female recruited as a potential participant was subsequently eliminated from the sample because she was found to have an IQ score within the average range.

All of the participants in the study were from eastern Sicily. All children with fragile X or RS, and 75% of the children in the comparison groups, were attending a school for the handicapped. The remaining children from the comparison group attended a regular school but had resource teacher assistance (“teachers of support”).

Procedure

Each participant was administered an Italian adaptation of a Wechsler test of intellectual functioning; the Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 1967) was administered to children ages 3 to 5 years; the Wechsler Intelligence Scale for Children–Revised (Wechsler, 1974) was administered to children 6 to 16 years of age, and the Wechsler Adult Intelligence Scale (Wechsler, 1955) was administered to young adults over 16 years of age.

The range of IQ scores recorded was 40 to 75. The lowest score attainable on the Wechsler tests is 40; therefore, children with scores less than 40 were not differentiated from each other nor from those with a score of 40. A score of 40 indicates moderate mental retardation. All of the females with RS and 12 of the males with fragile X syndrome had mental retardation. One male with fragile X scored in the borderline range of intellectual functioning (70). All of the females and 9 of the 14 males in the comparison group had mental retardation; one male without fragile X had a below average low average score (85), and the 4 remaining males had IQ scores in the borderline range (70–75).

The parents of each participant were interviewed separately by two independent interviewers. A semistructured interview was developed to assess presence of current behaviors based on the 16 behavioral criteria for Autistic Disorder. Thus each of the 16 interview questions corresponded to an item from category A, B, or C of these criteria and was numbered accordingly. Additional probes related to these criteria were also included, and were presented only if a parent answered “yes” to a particular interview item. For instance, if the parent indicated that their child had abnormal speech content, the parent was asked if the child’s speech was echolalic. (See Ap-
If a parent answered “yes” to any single item, the parent was asked to rate the frequency or severity of the behavior (little, moderate, or very much). Responses to each question were recorded relative to the frequency of an abnormal behavior or to the extent to which an appropriate behavior was absent. Final ratings, based on a dichotomous scale (Present, Absent) were determined by the severity rating for the behavior. Abnormal behaviors described as occurring for a moderate amount of time or more were coded as present. Responses indicating only occasional engagement of an abnormal behavior were rated as absent; however, responses indicative of occasional engagement of an appropriate behavior were considered “present” (e.g., engages in pretend play only occasionally was rated present). Hence the rating was a conservative measure of a significant frequency or degree of an abnormal behavior, or of a significant degree of the absence of an appropriate behavior.

The two interviewers scored their responses independently. Initial agreement was reached for 90%. The interviewers discussed any items for which there was disagreement until consensus was reached. This procedure was employed to minimize subjective interpretation of the parents’ responses.

RESULTS

Three sets of analyses were carried out to examine the behavioral profiles between (a) males with fragile X syndrome and males without fragile X, (b) females with RS vs. female without RS, and (c) males with fragile X and females with RS. The frequency of each of the 16 target behaviors was compared across groups, in each case with a 2 × 2 contingency table. An additional question, a probe regarding the presence of echolalia, was analyzed separately. Due to the small samples and the corresponding small expected values for each of the four cells, Fisher’s Exact-Probability statistics were calculated. For each set of analyses, a preliminary analysis was conducted to assess Full-scale IQ (FSIQ) scores between theagematched groups. Nonparametric statistics were used for these preliminary analyses because the IQ scores were not normally distributed.

Fragile X Syndrome Group Versus Comparison Group

An unpaired nonparametric (Mann-Whitney) analysis revealed no main effect of group on FSIQ. A Fisher’s Exact-Probability statistic was calculated for each of the 17 interview questions, corresponding to items A1 through C5 (see Appendix) and the probe regarding echolalia. The results indicated a significant main effect of group among only three of these items. For two of the items, the frequency of the undesirable behavior was lower among the males with fragile X relative to the non-fragile X males with other neurological impairment. None of the fragile X males, in contrast to 43% of the non-fragile X males, was rated as being unaware of others’ feelings (A1), \( \chi^2(1) = 7.6, p < .02 \). Among the males with fragile X, only one (7%) was rated as unable to form peer relationships (A5); in contrast, 50% of males without fragile X received this rating, \( \chi^2(1) = 6.3, p < .05 \). Echolalia (related to B4) was present among 5 (36%) of males with fragile X and none of the males without fragile X, \( \chi^2(1) = 6.09, p < .05 \).

The remaining group differences did not reach statistical significance; in three of the five instances for which a behavior was at least twice as frequent in one group vs. the other group, the differences were in the direction predicted on the basis of previous studies. Specifically, 71% of males with fragile X, vs. 29% of the non-fragile X males, were described as having stereotypies (C1), \( \chi^2(1) = 5.14, p = .057 \). Distress over changes in the environment (C3) characterized 43% of males with fragile X versus one (7%) of the non-fragile X males, \( \chi^2(1) = 4.76, p = .077 \). A limited range of interests (C5) was described for 71% of males with fragile X and 29% of males without fragile X, \( \chi^2(1) = 5.14, p = .057 \). Absence of abnormal play (A4) and abnormal nonverbal communication (B2) occurred more frequently among males in the comparison group relative to males with fragile X, findings contrary to those reported elsewhere in the literature. This pattern of findings is likely to have been influenced by the prevalence of autism in the control group and the method of parent interview, as discussed below.

Rett Syndrome Group Versus Comparison Group

A Mann-Whitney U test revealed a significant main effect of group on FSIQ, \( U = 42.0, p < .05 \).
Autism in Fragile X and Rett Syndromes

This effect was due to the fact that all 12 females with RS scored ≤40 on the IQ test, whereas 4 of the females without RS had an IQ score between 40 and 65. Thus despite the significant difference in IQ scores across groups, each girl from both groups had mental retardation. A Fisher's Exact chi-square statistic was calculated for each of 13 of the 17 interview questions corresponding to items A1 through C5. Analyses were not carried out for three communication items (B4, B5, and B6, which correspond to abnormal speech production, abnormal speech form and content, and the ability to maintain conversation, respectively) nor for the probe regarding echolalia, because 11 of the 12 females with RS did not have or use verbal language. These questions were therefore deemed irrelevant for this population.

The results indicated a significant main effect of group among 4 of these 13 items, including the capacity for communication (B1), \( \chi^2(1) = 12.61, p < .001 \). A higher proportion of females with RS (83%) was rated as not having imaginative play, relative to females without RS (27%), \( \chi^2(1) = 7.34, p < .05 \). All of the females with RS were rated as manifesting stereotypic movements (C1) versus 27% of females without RS, \( \chi^2(1) = 13.38, p < .001 \). A limited range of interests or excessive interest in a single item (C5) was more common among females with RS (92%) than among females without RS (27%), \( \chi^2(1) = 9.99, p < .05 \). Although a higher proportion of females with RS (50%) were rated as having stereotypic behaviors (C4) relative to females without RS (9%), this observed difference did not reach statistical significance, \( \chi^2(1) = 4.54, p = .069 \).

Fragile X and Rett Syndrome Groups

To further address whether qualitative differences in autistic behavior profiles are indicated between the two genetic groups examined, the relative frequency of abnormal behaviors was examined as a function of these two groups. Ratings on the seven items for which a genetic group vs. comparison group difference was identified were compared across the two genetic groups, with the following exception: Echolalia was not examined because it was not applicable to the group of nonverbal girls with RS. Among the remaining six items, a main effect of group (fragile X vs. Rett) emerged for three items. In each case, the effect was in the direction of females with RS having a higher frequency of the behavior in question, relative to males with fragile X. Girls with RS were more likely to have no verbal communication, \( \chi^2(1) = 5.27, p < .05 \); and no imaginative play, \( \chi^2(1) = 6.00, p < .05 \), relative to males with fragile X; and were more likely to be rated as unaware of others' feelings \( \chi^2(1) = 7.22, p < .02 \).

DISCUSSION

This study represents a preliminary attempt to compare and contrast the specificity of autistic behavior profiles for fragile X and RS, and to address whether the behavioral profile of children with fragile X warrants a unique PDD classification. The results of this study are preliminary because they are based on parent reports of current behaviors only; because of the conservative, dichotomous scoring used to interpret the parent interview; and because they are based on a small group of individuals from a wide age range. Nevertheless, the data are in part consistent with a report on a larger group of males with or without fragile X (i.e., 34 matched pairs; Reiss & Freund, 1992), and are consistent with the well-established criteria for RS. The differences in autistic behavior profiles across the two disorders have potential implications for the appropriateness that either disorder be classified as a specific PDD, although definitive implications cannot be derived from these preliminary results alone.

Fragile X Syndrome

As was also reported for the males examined by Reiss and Freund, the males with fragile X in this study did not show deficits in skills related to social behaviors such as awareness of others' feelings, seeking comfort, and ability to imitate. In this study, none of the 14 males with fragile X lacked awareness of others' feelings despite the high frequency (43%) with which males in the comparison group were described as lacking this awareness. Across this and the Reiss and Freund (1990, 1992) studies, males with fragile X were no less likely to form peer relationships than were the males in their age-matched comparison group. Although the lack of play reported by Reiss and Freund was not reported in this sample of boys with fragile X, this appears due to the fact that the play question used in this study was not specific to social play. In this study, most of the males with
fragile X were reported to play regularly or on occasion, but the qualitative aspects of their play was not assessed.

Similarly, in this study, a surprisingly low prevalence of abnormal nonverbal communication was reported among the boys with fragile X. No specific communication deficits were indicated in the fragile X group, except for a higher frequency of echolalia. This is in sharp contrast to frequent reports in the literature of poor eye contact in males with fragile X. This finding may be due to the dichotomous scoring used (i.e., rating whether abnormal nonverbal communication was present or absent), and potentially to linguistic or cultural differences in interpreting this criteria or in acceptance of nonverbal communication variability.

No specific deficits were indicated in the fragile X group with respect to restricted interests or behaviors. Abnormal motoric and sensory behaviors occurred more frequently among males with fragile X relative to males without fragile X. Although not statistically significant, higher frequencies were reported for stereotypies, preoccupation with or attachment to objects, incidence of distress to changes in environment or routines, and a limited range or highly focused area of interest among males with fragile X than among males in the comparison group. The lack of consistency between these results and those reported earlier may very well be due to the smaller sample in this study (n = 14 pairs) vs. the study by Reiss and Freund (1992; n = 34 pairs) and the associated low statistical power, and the discrepancy in composition of comparison groups across the two studies. The incidence of autism was higher in the comparison group used in the present study, which may reflect a clinical ascertainment bias associated with the clinic through which these individuals were recruited.

Rett Syndrome

The contention that RS is an etiology of autism has not been as controversial as the fragile X-autism association. The results from this study, though preliminary, are consistent with this contention because they suggest that qualitatively different profiles of autistic behaviors are observed in Rett vs. fragile X groups. Whereas the group of females with RS did not have a higher frequency of abnormal behaviors (relative to girls in the comparison group) across the domain of social behaviors, the frequency of significant communication deficits is clear. Stereotypic body movements were reported for both Rett and fragile X groups, but the frequency of stereotypic behaviors was greater among females with RS (50%) than among males with fragile X (21%). Eight of the 12 females with RS (67%) met DSM-III-R criteria for autistic disorder, and only 1 of the females in the comparison group (8%) met these criteria.

Classification of Pervasive Developmental Disorders

The introduction of Rett Disorder in the DSM-IV category of Pervasive Developmental Disorder (APA, 1994, pp. 71-73) reflects the degree to which autistic-like behaviors prevail among girls with RS and also reflects the specificity of these behaviors with respect to the language impairment. The results of the present study are consistent with this argument. A similar distinction for fragile X syndrome has not been incorporated into the DSM-IV, but its inclusion was proposed (Waterhouse, Wing, Spitzer, & Siegel, 1992) because of the frequency of autistic-like behaviors among males with fragile X. This proposal was challenged (Fisch et al., 1994; Rutter & Schopler, 1992) in part because of the high number of males with fragile X who do not manifest autistic behaviors. A unique PDD distinction may be irrelevant to the fragile X diagnosis for several reasons, not the least of which is the fact that fragile X has a known, testable genetic etiology whose diagnosis does not depend on a set of established behavioral criteria. Moreover, despite the specificity of autistic behavior among fragile X males and females, these behaviors (a) are not seen in all children with the disorder, (b) range in severity across individuals with the disorder, and (c) may be seen among individuals with fragile X regardless of whether they meet DSM criteria for autistic disorder.

Although based on small samples and on parent reports, the preliminary findings from this study contribute toward the controversy regarding classification of fragile X syndrome as a specific subset of PDD. Further studies based on child observation are needed, utilizing a larger sample of children with fragile X, to address this controversy. Among the 14 males evaluated in this preliminary study, none of the 11 who did not have a diagnosis of autism met the DSM criteria for PDD. Unlike Rett syndrome, for
which a high prevalence of autistic behaviors contributes toward its inclusion as a PDD in DSM-IV, the frequency and number of autistic behaviors among males with fragile X does not appear to warrant such a distinction. The results from this preliminary study are consistent with this notion.

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APPENDIX

English translation of behaviors presented to parents of subjects, which represent DSM-III criteria for Autistic Disorder:

A. Qualitative limitations in social interaction
1. Is not aware of others' feelings
2. Does not seek comfort
3. Reduced or inappropriate ability to imitate
4. Absent or abnormal play (uses others as tools for play)
5. Incapable of establishing relationships with peers

B. Qualitative limitations in communication
1. No ability to communicate verbally
2. Nonverbal communication is abnormal (such as gazes or gestures used to initiate contact)
3. Absence of imaginative activity
4. Marked abnormality in speech production (volume, pitch, stress, accent, rhythm, intonation)
5. Marked abnormalities in speech form and content (immediate or delayed echolalia)
6. Incapable of initiating and sustaining conversation (not interested in what others say)

C. Marked limitation in repertoire of activity or interests
1. Stereotyped body movements (hand, head, body)
2. Persistent preoccupation with parts of objects or attachment to unusual objects
3. Marked distress whenever minimal change occurs in the environment or in rituals
4. Stereotyped behaviors
5. Limited interests and/or an excessively narrow interest

REFERENCES


