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Problem Behavior in Boys With Fragile X Syndrome

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This study examines problem behavior over time in 59 boys with fragile X syndrome (FXS), aged 4–12 years, using the Child Behavior Checklist (CBCL). Approximately 49% of the boys scored within the borderline or clinical range on total problem behavior, while 56–57% scored in the borderline or clinical range on the attention and thought problems subscales, and 26% scored in this range on the social problems subscale. With a mean of 2.5 assessments per child, behavior problems were stable during the 3-year period of study. Total problem behavior was higher for children who displayed autistic behavior, were rated as low in adaptability, had mothers with higher maternal education levels, and were on medication. Mothers with more education also rated their children as having more attention, thought, and total problems. Children taking medication differed from boys who were not taking medication on social problems, but not on attention and thought problems. Low adaptability and more autistic characteristics predicted thought problems. © 2002 Wiley-Liss, Inc.

KEY WORDS: fragile X syndrome; behavior problems; Child Behavior Checklist

INTRODUCTION

Fragile X syndrome (FXS) is currently the leading known cause of inherited developmental disability with an estimated prevalence of 1:4,000 males and 1:8,000 females [Mazzocco, 2000]. Although the characteristics associated with the syndrome were first described decades ago, the gene itself was not identified until 1991. FXS results from a mutation of the fragile X mental retardation gene (FMR1) on the long arm of the X chromosome. In individuals with FXS, the number of trinucleotide repeats (CGG) in this gene becomes unstable and expands to 200 or more, considerably beyond that found in individuals without FXS (typically 6–50 repeats).

Males with full mutation FXS typically present with mild to moderate cognitive impairment, communication delays, and characteristic physical (i.e., a long face, large prominent ears, a narrow, high-arched palate, hyperextensible joints, and macroorchidism if postpubertal) and behavioral (e.g., hypersensitivity to sensory stimuli, eye gaze aversion, hand flapping, perservative speech) features. Although much of the early literature initially focused on the cognitive and intellectual disabilities evident in FXS, recent research has focused on behavioral challenges. However, little of this research has been reported on very young males with FXS [Kau et al., 2000; Mazzocco, 2000].

Early clinical descriptions [Hagerman, 1992; Lachiewicz, 1992a] provided some insight into behaviors observed in prepubertal boys. Hagerman [1992] reported that from 75–92% of boys younger than 13 years exhibited hand flapping, tactile defensiveness, poor eye contact, hyperactivity, tantrums, and perseveration. In a controlled study comparing boys with FXS to boys referred for FXS assessment but who did not have FXS, Lachiewicz [1992a] reported that tactile defensiveness was twice as prevalent in the boys with FXS.

In a study of phenotype and genotype correlations, Merenstein et al. [1996] examined the behavioral characteristics of prepubertal boys (mean age, 6.5 years), comparing boys with a fully methylated full mutation (FMFM) to those with a partially methylated full mutation (FMPM) and to those with mosaic patterns (both full mutation and premutation cells present). Across all three groups, high rates of several problem behaviors were observed: hand flapping (80–89%), hyperactivity (60–96%), perseverative behavior (60–95%), anxiety (53–75%), and poor eye contact (80–88%). Some differences in behavior as a function of genetic category were found—60–75% of the boys with FMFM and FMPM exhibited shyness, while only 44% of the boys with mosaicism showed this characteristic;

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64% of boys with FMFM exhibited hand biting, while only 40–42% of boys with mosaicism or FMPM did; only 25% of boys with FMPM exhibited tactile defensiveness, while 73–76% of boys with FMFM and mosaicism did. These findings suggest that there may be a link between genetic characteristics and behavior.

Poor eye contact, hand flapping, hand biting, and perseveration observed in prepubertal boys have led to questions regarding autism in FXS. Numerous studies have examined this question from a variety of perspectives. In a controlled study of 34 boys between the ages of 3 and 18 years matched on age and IQ, Reiss and Freund [1992] reported that males with FXS showed significant deficits in social play, nonverbal communication, and repetitive motor behaviors and a trend for abnormal responsivity to sensory stimuli, including oversenstivity to sound and elevated mouthing/smelling of objects. They found no differences in affective awareness, use of caregivers to seek comfort, or imitation. In another controlled study of 23 prepubertal males with FXS, Borghgraef et al. [1987] reported that males with FXS had significantly increased relational disturbances, aversion to gaze, and atypical eye gaze, compared to age-matched peers with nonspecific mental retardation. Similarly, Einfeld et al. [1999] found that behavioral and emotional problems of boys with FXS differed from children with general intellectual disabilities on behavior traits traditionally associated with autism, such as avoiding eye contact, antisocial behavior, and social shyness. Prospective studies of children with FXS suggest that approximately 25% either exhibit autistic characteristics or meet diagnostic criteria for autism [Turk and Graham, 1997; Bailey et al., 1998]. More recently, in a controlled study, Rogers et al. [2001] reported that 38% of a sample of 13 toddlers with FXS met stringent diagnostic criteria for autism.

In a recent series of studies, Bailey et al. [2000, 2001] examined autistic behavior in a sample of young boys with FXS (mean age, 64.1 months). Bailey et al. [2000] found that boys with FXS exhibited relatively flat profiles across developmental domains, while boys with autism, matched on age and ethnicity, showed lower scores on communication and social development. Children with both FXS and autism showed poorer developmental outcome than either boys with FXS or boys with autism. In a follow-up study [Bailey et al., 2001], autistic behavior was found to be more predictive of developmental outcome than the amount of FMR protein produced in blood cells.

The shyness and anxiety reported clinically have prompted further study of social anxiety in individuals with FXS. As mentioned above, Merenstein et al. [1996] reported high rates of anxiety in prepubertal males. In addition, Mazzocco et al. [1997] found positive correlations between anxiety and abnormal communication and social behaviors in girls with FXS. In a study of 18 males with FXS between the ages of 16 and 64 months, Freund et al. [1995] found that the mean scores on the social withdrawal scale of the Child Behavior Checklist (CBCL) were significantly higher than scores on the other subscales. Van Lieshout et al. [1998] found that the boys with FXS were less open to new experiences and less emotionally stable than a comparison group of typical children, but were not significantly different from boys with either Williams or Prader-Willi syndrome.

Attention deficits and/or hyperactivity have also been reported in boys with FXS. In a controlled study of males with FXS with a mean age of 8.7 years, Baumgardner et al. [1995] reported that approximately 73% of the boys with FXS met diagnostic criteria for attention deficit hyperactivity disorder (ADHD), compared to 33% of their age- and IQ-matched peers. Additionally, boys with FXS were distinguished by higher ratings of hyperactivity, inappropriate speech, and stereotypic behaviors, with this behavior profile more clearly described by teachers than reported by parents. The authors suggested that the problem behaviors specific to boys with FXS in this study, namely, hyperactivity, distractibility, perseverative speech, and stereotypic behaviors, might be related to information processing deficits that would also contribute to social problems. Freund and Reiss (unpublished manuscript) reported that 25 males between the ages of 5 and 18 years exhibited significantly greater impulsivity on an attention task than age- and IQ-matched peers. More recently, Turk [1998] found that boys with FXS scored significantly higher on an item on the CBCL that tapped restlessness and hyperactivity than boys with Down syndrome or nonspecific cognitive impairments. Further support for ADHD characteristics was provided by Van Lieshout et al. [1998], who reported that boys with FXS showed lower concentration and dependability in task situations than both typical peers and boys with Prader-Willi syndrome.

Temperament dimensions are also important traits to consider when examining the problem behaviors of boys with FXS. Temperament is typically considered to be at least partially genetic, as it appears to be present at birth and tends to remain relatively stable over time. Temperament constantly interacts with the environment leading to the development of a particular behavior style [McDevitt and Carey, 1978b]. Relatively little research has been done examining temperamental traits and problem behavior in children with disabilities. Interestingly, most studies of temperament in children with disabilities suggest that when compared to a reference sample of typically developing children, there are few differences [Brooks-Gunn and Lewis, 1982; DiLavore, unpublished dissertation; Gunn and Berry, 1985].

Two studies have examined behavior and temperament in young boys with FXS under the age of 8 years. Hatton et al. [1999] found that when compared to a typical reference sample, boys with FXS were significantly more active and less adaptable, approachable, persistent, and intense and that these characteristics were stable during the 3- to 8-year age span. The higher activity level and lower persistence are consistent with the ADHD studies of older children with FXS, while the lower adaptability and approachability might reflect autistic traits. In a controlled study of males between 3 and 6 years of age, Kau et al. [2000] reported that poor

motor skills, increased initial avoidance, decreased social withdrawal, and positive mood distinguished preschool-aged boys with FXS from age- and IQ-matched controls. However, the control group of age- and IQ-matched peers had been referred to a clinic for behavioral disorders, limiting the comparisons related to social withdrawal and mood.

Additionally, two studies have used the previous version of the Achenbach CBCL [Achenbach and Edelbrock, 1983]. Rather than summarizing the behavioral characteristics of boys with FXS, Turk [1998] compared their problem behaviors to children with cognitive impairment and children with Down syndrome. In this study, boys with FXS and the boys with cognitive impairments were reported to have significantly more problems overall and scored significantly higher on an item tapping nervousness or feeling tense than the Down syndrome group. The same analyses were also run using the teacher version of the CBCL, referred to as the Teacher Report Form (TRF) [Achenbach, 1991c]. Using the TRF, children in the FXS group were found to have more problem behaviors and a significantly higher total problem score, and they scored significantly higher on an item tapping restlessness and hyperactivity than children with either Down syndrome or cognitive impairments. Lachiewicz [1992a] described problem behavior in girls using the earlier version of the CBCL. Approximately 47% of the girls with FXS had clinically significant scores on the hyperactive and social withdrawn scales, and between 15% and 26% of the girls also had clinically significant scores on the depressed scale, schizoid-obsessive scale, schizoid or anxious scale, and the aggressive scale. No means for these subscales, the total problem score, internalizing score, or externalizing score were reported.

More recently, Freund et al. [1995] and Kau et al. [2000] have described the performance of children with FXS on specific subscales of the latest version of the CBCL. When controlling for maternal avoidance/approach, Kau et al. [2000] reported significantly lower levels of withdrawal behavior in 41 preschool-aged boys than among the age- and IQ-matched controls who had been referred to a behavior disorders clinic. Freund et al. [1995] found that their 18 subjects between the ages of 16 and 64 months scored significantly higher on the social withdrawal scale than the aggression, depression, and destruction subscales of the CBCL (2- to 3-year-old version).

A related instrument, the Developmental Behavior Checklist [Einfeld and Tonge, 1995], was used to compare the behavior of children with FXS to other children with mental retardation (MR). In a longitudinal study comparing behavior over a 7-year period, Einfeld et al. [1999] reported no significant difference in the overall behavior of children with FXS over time. However, there was a decline in scores on the disruptive subscale and an increase in the antisocial subscale. Compared to a group of children with nonspecific MR, the children with FXS had significantly fewer problem behaviors at both points in time. The children with FXS, however, avoided eye contact and appeared shy significantly more than children in the MR group at both points in time. Also compared to the MR group, the children with FXS became more self-absorbed and scored lower on the social relating subscale.

Whether or not challenging behavior in boys with FXS is related to cognitive impairment or to family characteristics is also of interest. Hatton et al. [1999] found that neither developmental quotient nor maternal education was related to temperament ratings of boys with FXS. Bailey et al. [1998] also reported that there was no relationship between maternal education and ratings of autistic behavior in boys with FXS, but there was an inverse relationship between developmental quotients and ratings of autistic behavior. Baumgardner et al. [1995] reported that IQ was not related to behavior problems and that IQ scores and the Vineland Adaptive Behavior composite scores were highly correlated. Van Lieshout et al. [1998] found that low parental consistency was related to more anger in parents and that greater anger resulted in lower agreeableness, lower conscientiousness, lower emotional stability, lower openness, and higher irritability in boys with FXS (mean age, 10.5 years).

From a clinical perspective, behavior can often present greater challenges than cognitive delays in children with FXS. Parents and professionals often report that challenging behaviors are their greatest concern regarding their child with FXS [Hagerman, 1996b; Hatton et al., 2000]. Perhaps one of the most striking indicators of these problems is the extensive use of medications with FXS children, sometimes at very young ages [Tranfaglia, 1995; Hagerman, 1996a].

In estimating the effectiveness of stimulants, one study reported that attention and sociability were improved in boys with FXS on a trial of methylphenidate [Hagerman et al., 1988]. Interestingly, the effectiveness of stimulants may be related to intellectual ability and, more specifically, may not be effective in children with severe mental retardation. For example, Aman et al. [1991] found that children with an IQ of 45 or below had poor response to methylphenidate.

The effectiveness of a number of other medications has been documented for children with FXS. Hagerman et al. [1994] reported results from a study on the effects of a selective serotonin reuptake inhibitor (SSRI), fluoxetine specifically, on both males and females with FXS. The overall behavior of most of the males was much improved, with specific improvements noted in aggression, hyperactivity, depression, and self-abuse. For girls, there was improvement in depression, mood lability, outburst behavior, panic attacks, obsessive-compulsive symptoms, and anxiety. Another study documented the improvement of ADHD symptoms in three males with FXS following a trial of clonidine [Leckman, 1987]. More recently, Hagerman et al. [1995] found that the behavior of 63% of a sample of children with FXS improved on the sympatholitic, clonidine, with the highest occurrence of improvement in hyperactivity. An important factor to mention is that most of the children were also taking other medications during this study, including methylphenidate and/or carbamazepine, which is likely to have had a confounding effect on these results.

Two studies documented the effectiveness of tricyclics in children with FXS. Hilton et al. [1991] documented the successful use of imipramine for reducing hyperactivity, increasing attention, and improving insomnia and enuresis in a boy with FXS. Hagerman [1996a] reported that although imipramine worked on several patients with FXS, it increased aggressive or outburst behavior in others. She hypothesized that this was related to mood instability in FXS, which could be exacerbated by imipramine.

From this review, it is apparent that researchers and clinicians from the disciplines of pediatrics, psychology, psychiatry, and education have used varied methods to examine behavior in children with FXS. Many of the behaviors seem to cluster into two groups, autistic traits and ADHD traits. Additionally, some children appear to have social withdrawal and shyness that may or may not be related to autistic traits. In most cases, researchers studied behavior at one point in time, not longitudinally.

Therefore, we were interested in studying problem behaviors longitudinally in young boys with FXS across a restricted age range using a measure that taps as many of the problem behaviors cited in the literature as possible. This article reports a study of problem behavior of boys with FXS using the CBCL for the following reasons: 1) many of the behaviors described in the literature often fall within the realm of psychiatry and psychology, and the CBCL is widely used in those disciplines; 2) the CBCL describes behaviors using eight categories or syndrome subscales, allowing us to determine the types of behaviors that appear most problematic using one instrument; and 3) the CBCL is designed for children between 4 and 18 years, making it ideal for a longitudinal study.

In particular, the withdrawn and anxious/depressed subscales should tap dimensions of behavior related to social withdrawal and/or anxiety. The thought problems subscale should tap autistic behaviors, such as repetitive and compulsive behaviors. The attention problems subscale should capture ADHD traits, while the delinquent and aggressive subscales should capture externalizing behaviors directed toward others. The following questions served as the basis for our study:

1. Do boys with FXS score in the clinical range on the summary scales and subscales of the CBCL? Based on the existing literature, we would expect boys with FXS to score in the clinical range on the following subscales: withdrawn, anxious/depressed, social problems, thought problems, and attention problems.
2. What categories of behavior appear most problematic for young boys with FXS? Again, we would expect the syndrome subscales listed in the first question to be most problematic; however, we do not have adequate background information to predict which subscale will be most problematic.
3. Do boys with FXS show significant changes in behavior over time, as measured by summary and subscales of the CBCL? Because only one study reported in the literature was longitudinal [Einfeld et al., 1999], we have little basis for predicting stability. However, those authors found no significant changes in behavior over a 7-year period, and so we predict that behavior problems will be stable over time in our sample.
4. What variables predict scores on summary scales and subscales of the CBCL? Based on the literature, we predict that maternal education, temperament, autistic behavior, and medication status will influence both the overall and subscale scores, while developmental status will not influence outcome.

MATERIALS AND METHODS

Participants

The participants were 59 males with FXS in four southern states. All of the participants were diagnosed with full mutation FXS using DNA analyses. Demographic characteristics of the participants are shown in Table I.

Subjects were recruited through genetics clinics, developmental evaluation centers, and early intervention programs. Informed consent for participation was obtained from the parents or guardians of all participants. For each assessment period in which the child/family participated, families received a $25 stipend and a brief summary of the developmental assessment and behavioral observations made by project evaluators.

Instrumentation

Behavior assessment. The CBCL for ages 4–18 years is a parent-report instrument used to provide a standardized procedure for assessing behavioral and emotional characteristics in children [Achenbach, 1991a, 1991b]. The items on this scale targeting different problem behaviors are rated as not true (0), somewhat or sometimes true (1), or very true or often true (2). Raw scores on this measure are converted into percentile ranks and T-scores in order to compare an individual child's results to the normative sample. The 113 items make up eight subscales, or syndrome scales. These subscales are withdrawn, somatic complaints, anxious/depressed, delinquent behavior, aggressive

TABLE I. Description of Participants (N = 59)

Characteristics	
Age	
Mean age (months)	86.60
Standard deviation	24.24
Range (months)	48–152
Ethnicity	
European American	52 (88.1%)
African American	6 (10.2%)
Hispanic	1 (1.7%)
Mother's education	
High school graduate or less	27 (45.8%)
Some college	20 (33.8%)
College degree or higher	12 (20.4%)
Medication status	
Off	22 (37.3%)
On	37 (62.7%)

behavior, social problems, thought problems, and attention problems. T-scores on the syndrome scales between 67 and 70 are considered to be in the borderline range, while T-scores above 70 are in the clinically significant range. The items from the withdrawn, somatic complaints, and anxious/depressed syndrome scales are used to make a broad grouping referred to as the internalizing problem score, while the items from the aggressive behavior and delinquent behavior syndrome scales comprise the externalizing problem score. Finally, an overall composite score is gained from all items on the CBCL and is referred to as the total problems score. T-scores for total problems, internalizing problems, and externalizing problems between 60 and 63 are considered to be in the borderline range, while T-scores above 63 are in the clinically significant range (90th percentile).

The CBCL has also been used in a number of studies of children with disabilities, as shown in Table II. Although the studies span a wide range of disabilities and the results are complex, in general, it appears that these samples of children with cognitive impairments display different patterns of scores on the CBCL than do typically developing children and children with psychopathology.

Temperament assessment. The Behavioral Style Questionnaire (BSQ) [McDevitt and Carey, 1978a] was used to measure behavioral style [Carey and McDevitt, 1995]. The scale has a high level of internal consistency (.84) and test/retest reliability (.89) [McDevitt and Carey, 1978b]. Parents are asked to respond to 100 items (e.g., the child is slow to adjust to changes in household rules) on a 6-point rating scale, ranging from 1 (the child almost never demonstrates a particular behavior) to 6 (the child almost always exhibits that behavior). Item ratings generate scores for the nine temperament dimensions identified by Thomas et al. [1963]. Scores from the following dimensions were included in our analyses: activity, approach, adaptability, and persistence/attention. These dimensions were included because boys with FXS have been reported to exhibit atypical behavior on these scales [Hatton et al., 1999].

Adaptive behavior assessment. Adaptive behavior was assessed using the Vineland Adaptive Behavior Scales, Interview Edition (VABS) [Sparrow et al., 1984]. The VABS is a widely used measure, providing a general assessment of adaptive behavior from birth to 18 years of age. This measure consists of 297 items tapping communication, daily living skills, socialization, and motor skills. It is administered through a semistructured interview with the parent.

Autistic behavior. Autistic behavior was assessed using the Child Autism Rating Scale (CARS) [Schopler et al., 1988]. The CARS consists of 15 items that tap a range of behavioral and physical responses, such as imitation, adaptation to change, fear or nervousness, verbal and nonverbal communication, activity, and intellectual response. These items are rated on a scale from 1 (within normal limits for age) to 4 (severely abnormal for age). Total scores below 30 are considered nonautistic, scores between 30 and 36.5 translate to mildly or moderately autistic, and scores of 37 or higher indicate the child is severely autistic.

Procedures

As part of data collection for a longitudinal study of development and education of boys with FXS, parents were asked to complete the CBCL and the BSQ on an annual basis. The forms were discussed with the parents who were asked to complete and return them. A stamped, self-addressed envelope was included with the forms to make returning the information convenient. If forms were not returned within 4 weeks, a reminder follow-up letter and/or phone call was made. New forms were mailed if parents could not locate the original scales.

The CBCL scores were the dependent variables in all analyses. The CBCL data reported represent a total of 150 assessment occasions, for an average of 2.5 assessments and a range of 1 to 4 ratings per child obtained between 1997 and 2000. For children with multiple assessments, the average length of time between assessments was 14.1 months (SD = 4.0). Only maternal ratings were used for this analysis. Independent variables included chronological age, the four scales from the BSQ, the adaptive behavior composite score from the Vineland, the total score from the CARS, medication status (on or off and type of medication), and maternal education.

Data Analysis

A variety of statistical techniques were used to analyze the data. Data were screened for normality and descriptive summaries were generated. Hierarchical linear modeling and descriptive summaries were used to answer our research questions. Advantages of this approach include simultaneous estimation of individual and population growth curves under the assumption that the individual curves are systematically distributed about the population curve. This approach can be used even when individuals have randomly missing data or when time-varying covariates are of interest.

The analyses were run in two steps. In the first step equations for means and slopes were estimated for each of the six CBCL scores of interest (total, internalizing, externalizing, thought problems, social problems, and attention problems). In the second step, fixed effects were estimated for a set of explanatory variables for each of the six CBCL scores. The explanatory variables were of two types: scores assessed once for each child and scores assessed on multiple occasions for each child (time-varying covariates). The explanatory variables assessed once were CARS total scores, temperament scales (activity, approach, adaptive, and persistence), and mother's education level. The time-varying covariates were medication status and Vineland Adaptive Behavior composite scores.

RESULTS

Using hierarchical linear modeling, we found that CBCL scores, both summary and syndrome, were stable

TABLE II. Use of the CBCL With Children With Disabilities

Title	Reference	Subjects	N	Age	Findings
Patterns of parent-reported problems indicative in autism	Bolte et al. [1999]	Males and females with autism	77	4–18	Higher relative scores on social problems, thought problems, and attention problems than normative and clinical samples.
Measuring problem behaviors in children with mental retardation: dimensions and predictors	Borthwick-Duffy et al. [1997]	Children and adolescents with MR	67	8–20	Higher order dimensions (internalizing and externalizing) were similar to standardization sample, first-order factors not found in this sample.
Maladaptive behavior in children with Prader-Willi syndrome, Down syndrome, and nonspecific mental retardation	Dykens and Kasari [1997]	Children with Prader-Willi, Down syndrome, and nonspecific MR	129	4–19	For the nonspecific MR, males had more externalizing problems than females. IQ was not correlated with CBCL results for any group. In Down syndrome, age was associated with internalizing problems, anxiety and withdrawal. Prader-Willi subjects had higher scores in internalizing, externalizing and total problems and more clinically significant scores than the other two groups.
Adaptive and maladaptive behavior in Prader-Willi syndrome	Dykens et al. [1992]	Children with Prader-Willi syndrome	21	13–46	Adolescents had significantly higher scores on externalizing than the two older groups.
Distinctiveness and correlates of maladaptive behavior in children and adolescents with Smith-Magenis syndrome	Dykens and Smith [1998]	Children and adolescents with Smith-Magenis syndrome	35	4–20	Smith-Magenis group scored in the clinically significant range for total problems. Also elevated scores for aggression and other. Higher than mixed comparison group, but not Prader-Willi comparison group on social problems, thought problems and somatic complaints. Examination of item level behaviors provided further description.
Cognitive, adaptive, and behavioral characteristics of Williams syndrome	Greer et al. [1997]	Boys and girls with Williams syndrome	15	4–18	Clinically significant scores on attention problems across the subjects. Borderline scores for thought problems and social problems. IQ and adaptive behavior scores in the low 60's to low 70's.
Neuropsychological and neurophysiological indices of auditory processing impairment in children with multiple complex developmental disorder (MCDD)	Lincoln et al. [1998]	Children with behavior disorder (BD)/MCDD and ADHD + normal controls	30–40	9–13	In both experiments the children with BD/MCDD had clinically significant total problem, internalizing, and externalizing behavior scores. Clinically significant elevations on all subscales. These were significantly higher than the ADHD and control samples.
Cluster analytic identification of autistic preschoolers	Rescorla [1988]	Boys with autism or autistic-like behavior plus controls with other psychiatric disorders	204	3–5	Using cluster analysis a number of items on the CBCL were found to be useful in the identification of autistic traits. This cluster of items was identified by the author as autistic/bizarre.
Problem behaviors and personality of children and adolescents with Prader-Willi syndrome	van Lieshout et al. [1998]	Children and adolescents with Prader-Willi syndrome	39	3–20	Total problem scores did not differ from reference group (MH clients) less anxious, depressed, aggressive. Higher scores on thought problems, social problems, and obesity.

over time (with the P values for age at assessment ranging from .346–.837). In other words, rather than increasing or decreasing over time, they remained flat, resulting in a horizontal "growth curve" for problem behavior. For that reason, we used an average of scores across assessment occasions as a summary score for each child when examining summary and subscale scores on the CBCL.

Next, we examined the performance of boys on total problem behavior, as well as on externalizing and internalizing problems. Although the mean score for the sample on total problem behavior was 60.08, which is in the borderline range, 44% of the boys in the sample scored within the clinical range (> 64). The mean scores for internalizing problems (53.9) and externalizing problems (53.5) were within the average range; however, 17% of the boys in the sample scored in the clinical range on internalizing problems, as did 19% of the boys on externalizing problems, with 8% of the boys scoring in the clinical range on both scales. In Figure 1, the percentages of boys who scored in the borderline and clinical ranges are shown.

The mean scores for the syndrome scales of the CBCL are plotted in Figure 2. The solid horizontal line represents the mean for the reference sample of the CBCL, while the dashed lines represent 1 SD above and below the mean. Again, the mean scores for the current sample were within the average range for all syndrome scales, except social problems, thought problems, and attention problems. As can be seen in Figure 3, from 26–57% of the boys in the sample scored in the borderline or clinical range on these three scales. Thought problems and attention problems appear to be the most severe problem behaviors in our sample. In order to identify factors that predict scores on the CBCL, we used hierarchical linear modeling to analyze our longitudinal data set. Child age, maternal education, the adaptive behavior composite score from the VABS, scores from the BSQ temperament dimensions of activity, adaptability, approach, and persistence/attention span, and scores from the CARS were used as independent variables.

Total problem behavior scores were related to autistic behavior (CARS scores, $P = .028$), the temperament dimension of adaptability ($P = .002$), medication status ($P = .019$), and maternal education ($P = .005$). Internalizing scores were predicted by adaptability ($P = .010$) and medication status ($P < .001$), while externalizing problems were predicted by adaptability ($P < .001$). Predictors for three syndrome scales were also identified. Thought problems were predicted by autistic behavior ($P = .011$), adaptability ($P = .044$), and

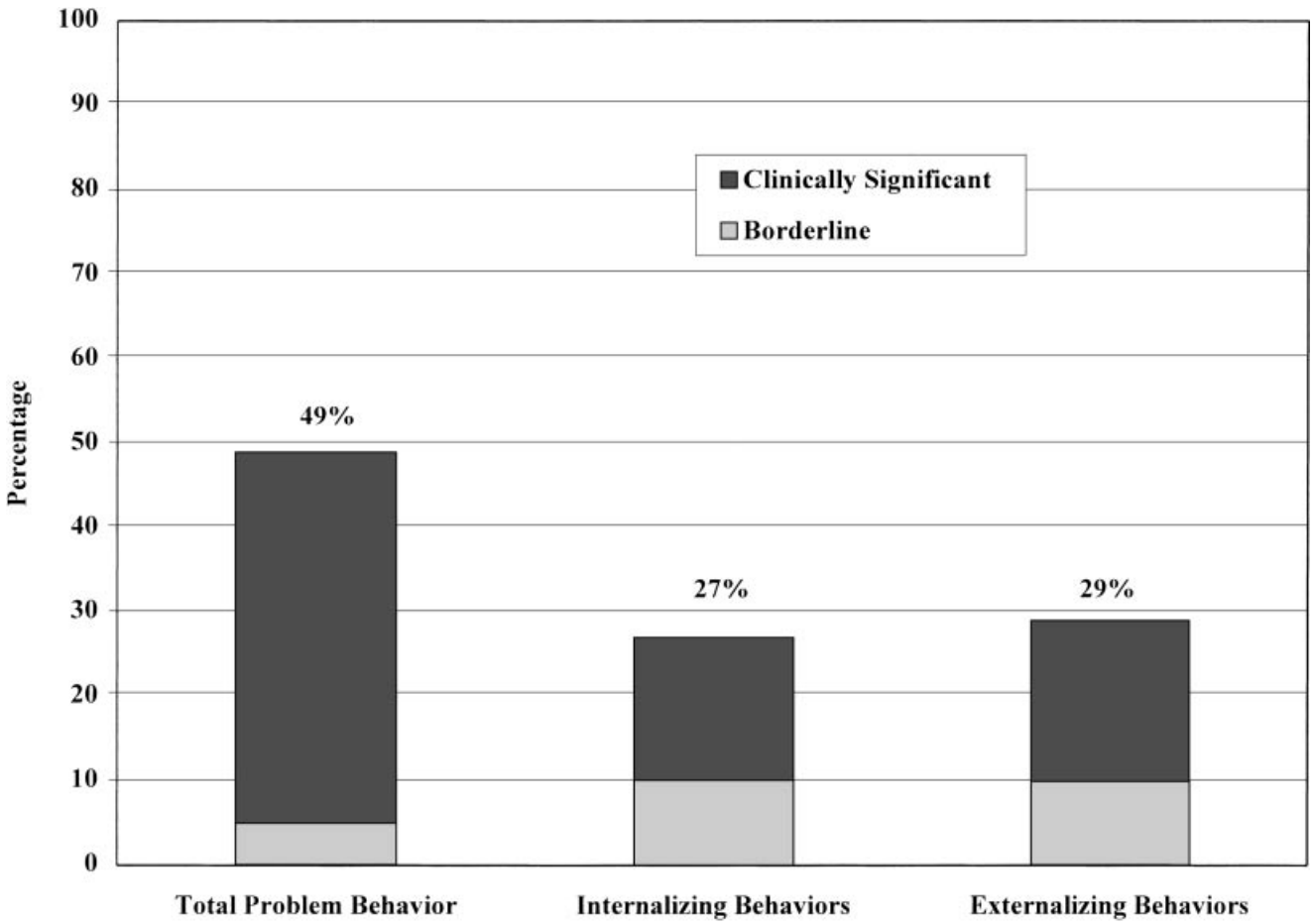

Fig. 1. Percentage of boys with FXS in the borderline or clinically significant range on CBCL scales.

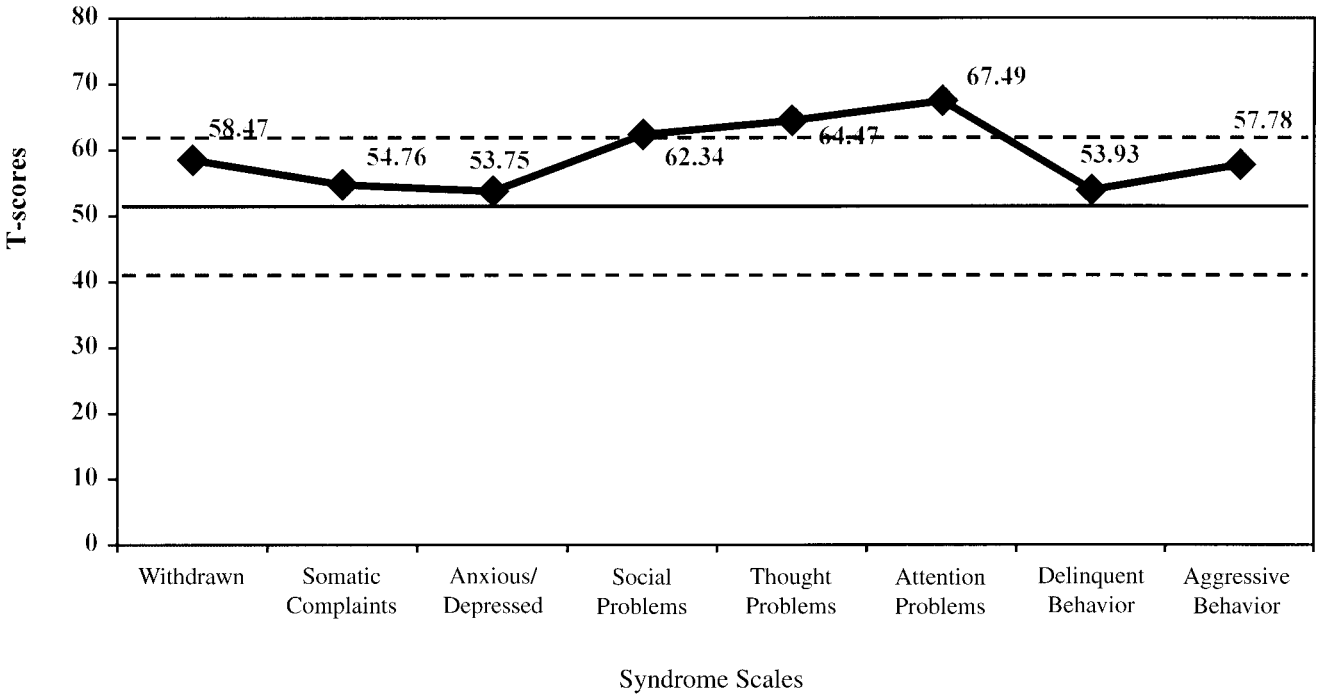

Fig. 2. Mean scores for boys with FXS on the syndrome scales of the CBCL.

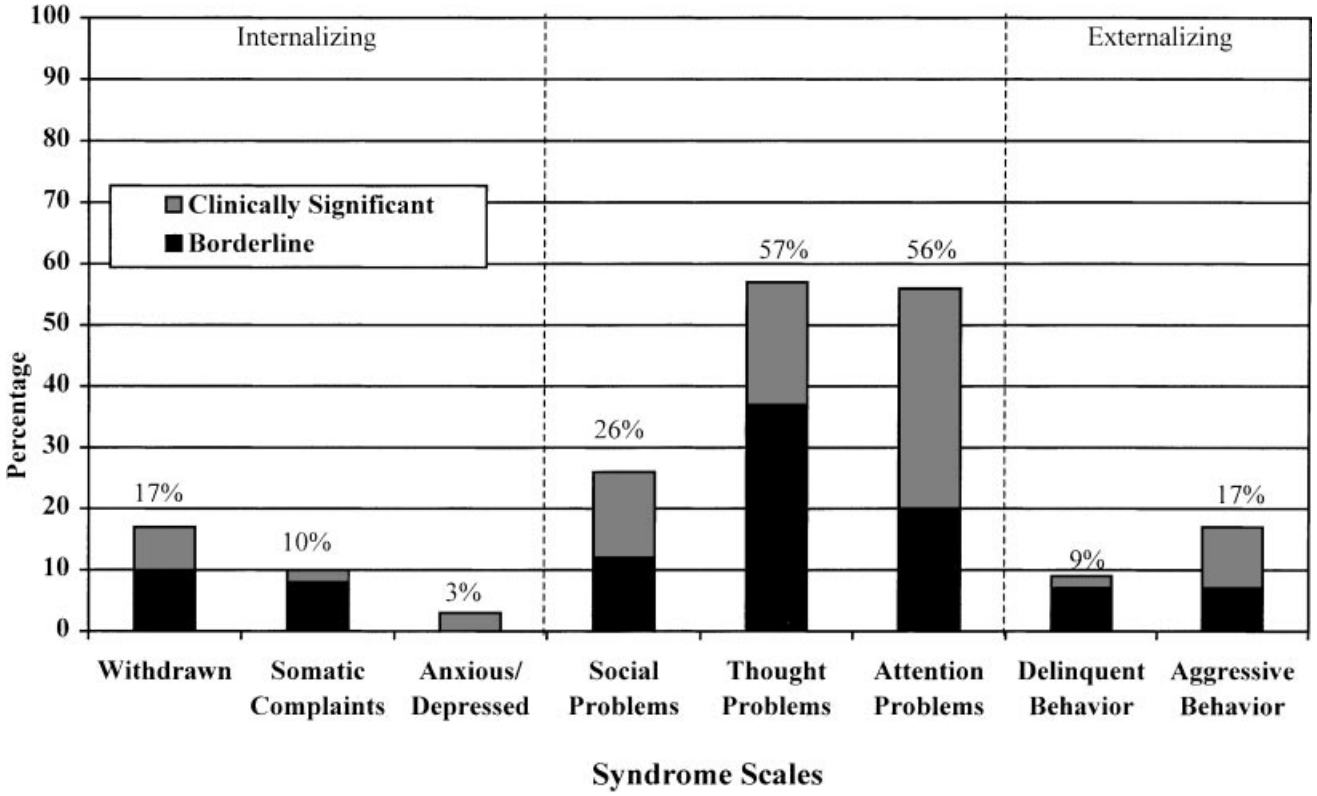

Fig. 3. Percent of boys with FXS who scored in the borderline or clinically significant range on the syndrome scales of the CBCL.

maternal education ($P = .018$). Social problems were predicted by autistic behavior ($P = .035$) and medication ($P = .041$), and attention problems were predicted by maternal education ($P = .003$). In all cases, children who were on medication had higher problem behavior scores. Mothers with college education or higher rated their children as having more problems than did mothers with less education. Higher CARS scores reflect more autistic behavior and were associated with more problem behavior. Likewise, low adaptability scores were associated with more problem behavior.

There were no significant differences between children on or off medication on externalizing behavior, thought problems, and attention problems. In contrast, children who were on medication received higher scores on total problems, internalizing problems, and social problems than children not on medication. In an effort to learn as much as possible about the medication status of the participants, we ran additional analyses to compare the performance of children taking varying types of medication. Unfortunately, because of the high variability in the types of medication used, there were insufficient numbers of children on particular medications to make meaningful comparisons. However, we were able to compare the scores of children who were taking stimulants, sympatholytics, other medications (any medication other than stimulants or sympatholytics), or no medication. The only significant finding was that stimulants were associated with more internalizing problems ($P = .003$). Many children were on varying combinations of medications, again limiting our ability to identify specific relationships between types of medication and its impact on CBCL scores.

Adaptive Behavior composite scores, a marker for developmental status or level of disability in this study, were not associated with problem behavior. The temperament dimensions of activity, approach, and persistence/attention were also not associated with problem behavior.

DISCUSSION

Results from this study suggest that the CBCL provides useful information about the behavior of boys with FXS. Consistent with other studies of development and behavior of children with FXS, we found considerable variability in our sample that would have been masked had we examined only mean scores. Indeed, mean scores for the sample were within the average range for internalizing and externalizing problems and for all syndrome scales, except thought problems, social problems, and attention. However, 26–57% of the sample scored in the clinical range on total problem behavior and on the thought, social, and attention problems subscales. Thought and attention problems appeared to be more severe than the other six categories.

The mean scores obtained on this sample of boys (mean age, approximately 7 years) were similar to those reported in Kau et al.'s [2000] sample of boys between the ages of 3 and 6 years. Specifically, we obtained a score of 67.5 on attention problems, compared to 67.1 reported by Kau et al.; a score of 58.5 on withdrawal, compared to 55.9 reported by Kau et al.; a score of 53.8 on anxious/depressed, compared to 52.9 reported by Kau et al.; and a score of 54.8 on somatic complaints, compared to 54.1 reported by Kau et al. The similarity in the scores of the two samples of young boys with FXS is striking. (Kau et al. did not report mean scores for the remaining syndrome subscales of the CBCL.)

Scores on the CBCL were stable over time and could be predicted by autistic behavior, adaptability, medication status, and maternal education. Interestingly, the temperament dimensions of activity, approach, and persistence/attention were not significant predictors of CBCL scores, and neither was adaptive behavior status. While problem behavior appeared stable over the course of time, the time period under study was approximately 3 years, and the boys' age range is relatively restricted (48–152 months). It will be interesting to see if behavior remains stable over a greater age range as the boys grow older.

Autistic behavior influenced total problem scores and thought and social problems, but not internalizing or externalizing summary scores nor scores on attention. Bolte et al. [1999] reported elevated scores on social problems, thought problems, and attention problems in their sample of 77 children with autism. Differences on the attention subscale might be due to the relatively high percentage of children in our sample who are taking medication—stimulants in particular. Bailey et al. [1998, 2000] and Cohen [1995] reported that autistic behavior is associated with poorer developmental outcome in individuals with FXS. Our results suggest that it is also associated with increased problem behavior, as would be expected.

Low adaptability, one of the nine temperament dimensions measured by the BSQ, was also found to be related to total problem behavior, internalizing and externalizing behaviors, and thought problems. Again, this finding is not surprising; however, a lack of significant findings for social problems is intriguing, as is the lack of association of the temperament dimensions of activity, approach, and persistence/attention with any of the CBCL summary or syndrome scores.

Medication could be considered to be effective if no significant differences were found between children on and off medication. Therefore, it appears that medication was effective for externalizing behavior, thought problems, and attention problems because there were no significant differences between children who were and were not on medication. However, because this was not an experimental design with before and after data, this finding is speculative.

Because medication use typically results from challenging behaviors, it is not surprising that medication status is associated with scores on the CBCL. Further conclusions regarding medication use and the CBCL in this sample is not possible due to the following limitations: 1) medication status was documented on the basis of maternal report, 2) multiple medications were used for a variety of symptoms, 3) considerable variability in CBCL scores was evident in children on and off of medication, and 4) medication use varied over time. Because we used hierarchical linear modeling,

medication status could vary across observations. Therefore, we examined scores for each child across time, whether he was on or off medication. Documentation of the types and numbers of medications used in this sample of boys with FXS is noteworthy and illustrates the problems that will likely plague research on this topic.

An intriguing finding in this study is that mothers with college degrees reported higher levels of problem behavior in their sons. Palfrey et al. [1989] found similar results in a study on families of chronically disabled children. Mothers with higher education levels reported higher family stress and more behavior problems than mothers with lower educational attainment. The authors suggest three possible explanations for these findings: 1) higher educated parents may be better able to pinpoint their child's condition as a source of distress, whereas less educated parents may regard poverty, unemployment, or other stresses associated with lower education levels as the reason for their stress; 2) more educated families may be more willing to look for the etiology of stress in their families and to diagnose the child's disability as the source; 3) the discrepancy between the child's functioning and the parent's level of scholastic achievement may be felt more acutely by higher educated parents. Other possible explanations include the possibility that boys in this sample with the most problem behavior happened to be in families in which mothers have a college degree or higher. Or perhaps a combination and/or interaction of these factors influenced our results. This issue deserves further study.

When comparing the relationship between problem behavior and maternal education in samples of children without disabilities to children with disabilities, the results are inconsistent. In studies of children without disabilities, children whose mothers have higher levels of education have been shown to have higher IQs, greater academic competence, and less psychopathology [Werner et al., 1971; Broman et al., 1975; Kochanek et al., 1987; Palti et al., 1987; Velez et al., 1989]. In terms of behavior, Auerbach et al. [1992] found that among 505 Israeli kindergarten children without disabilities, there was a negative correlation between mother's education and problem behaviors as indicated on the CBCL. This indicates that the higher the mother's education the fewer problem behaviors reported. However, among parents of children in special education, a higher number of problems with their child and more family stress were reported by mothers who had a higher education level [Palfrey et al., 1989]. Thus, literature from the field does not provide an easy explanation of our findings.

Thought problems, social problems, and attention appear to contribute to the elevated total problem scores on the CBCL in this sample. The items on the thought problem scale tap the autistic-like behaviors that have been documented in individuals with FXS. The eye gaze avoidance and hyperarousal that have been described by numerous researchers and documented by differences in measures of sympathetic [Miller et al., 1999] and parasympathetic [Roberts et al., 2001] tone probably contribute to social problems, as do autistic behaviors. Finally, numerous clinicians and researchers have documented problems with attention. The large number of children who are taking medication in this sample attests to the significance of attention and attention-related problems in children with FXS.

Because the CBCL factor structure was developed from a clinical sample of children and normed on a nonhandicapped sample, some have questioned the applicability of this instrument to children with mental retardation [Einfeld and Tonge, 1991; Turk, 1998]. Clearly, however, the CBCL was found to be applicable with a sample of boys with FXS because important relationships were found between environmental characteristics (i.e., maternal education), child characteristics, and behavioral problems in the present study. However, the next step in this line of research should be to repeat this research using the Developmental Behavior Checklist [Einfeld and Tonge, 1995] or a similar instrument having a factor structure based on a sample of children and adolescents with mental retardation, with the hopes that even clearer patterns of relationships between environmental, individual, and behavioral characteristics will emerge.

In addition, our challenge now is to design and execute focused studies that examine intervention to target the problem behaviors identified in this study and the variables associated with this behavior. The use of strategies appropriate for children with autism and attention deficit, controlled prospective studies of medication, and consistent use of behavior management by parents and teachers are possible interventions that might successfully address the challenging behavior seen in some children with FXS.

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