Journal of Autism and Developmental Disorders, Vol. 18, No. 3, 1988

Fragile X Syndrome: Genetic Predisposition to Psychopathology[1]

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Fragile X syndrome is a newly recognized X-linked disorder which has been associated with a high prevalence of psychiatric disturbance, particularly attention deficit disorder and autism. The present study involved the neuropsychiatric evaluation of 14 males with the disorder who were between the ages of 3 to 27 years. Pervasive hyperactivity, impulsivity, and attentional deficits were found among all of the subjects, while a significant degree of anxiety was manifested by more than half. Although the majority of subjects exhibited poor eye contact, atypical speech and language functioning, and stereotyped behavior, only one met DSM-III diagnostic criteria for a persistent pervasive developmental disorder. Gaze aversion, noted among half of the subjects, was attributed to underlying anxiety rather than to autistic social dysfunction because of the otherwise socially engaged and affectionate behavior exhibited by the subjects. Failure to make this distinction in the context of cognitive and linguistic impairments associated with fragile X syndrome may account for the high rates of autism reported by other investigators.

Fragile X syndrome is a recently described X-linked disorder which is surpassed only by Down syndrome as the most prevalent form of mental retardation of genetic origin. The syndrome is associated with a variable cllinical phenotype which includes a set of characteristic facial features (e.g., a thin,

[1]This research was supported in part by the John Merck Fund, NICHD Grant HD03008, CCRC Grant RR00125, and MHCRC Grant MH30929. The authors thank Fred Volkmar, Elisabeth Dykens, Robert Hodapp, and Wendy Marans for their comments and suggestions during the preparation of this manuscript.
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0162-3257/88/0900-0343$06.00/0

elongated facial contour, a prominent mandible, enlarged, poorly developed ears), as well as macroorchidism in affected males. Impairments in cognitive and language functioning are common.

Recent investigations of affected fragile X males have revealed a disproportionately high frequency of psychiatric disturbance, most commonly involving hyperactivity, attention deficits, and autistic symptomatology. Attention deficits and hyperactivity appear to be particularly common (Chudley & Hagerman, 1987). Three recent studies found that 41 of 50 subjects (82%) demonstrated these behavioral characteristics (Finelli, Pueschel, Padre-Mendoza, & O'Brien, 1985; Fryns, Jacobs, Kleczkowska, & Vanden Berghe, 1984; Largo & Schinzel, 1985).

Since fragile X males frequently manifest gaze aversion, language deviance (such as echolalia and perseveration), and behavioral abnormalities (such as stereotypic and self-injurious behavior), investigators have suggested that a relationship may exist between the fragile X syndrome and autism (Brown et al., 1982; Levitas, McBogg, & Hagerman, 1983). During the past 5 years, a number of reports have called attention to a potential relationship between these two syndromes. In the largest series, Brown et al. (1986) reported that 21% of 434 fragile X subjects (150 personally examined and 284 reviewed from the literature) were given autistic diagnoses. Other investigators have reported even higher rates. Hagerman, Jackson, Levitas, Rimland, and Braden (1986), for instance, found that 23 of 50 fragile X males (46%) met DSM-III (American Psychiatric Association, 1980) criteria for infantile autism, full syndrome or residual state.

Investigators, encouraged by this rather impressive association, have questioned whether fragile X syndrome may in fact represent a major etiology for autistic disorders. In an effort to explore this hypothesis, several studies have screened autistic subjects for the presence of the fragile X chromosome. Of 594 autistic males reported in 10 studies, 8.4% were found to express the fragile X site (Bregman, Dykens, Watson, Ort, & Leckman, 1987). However, the individual studies themselves reported rather disparate findings. Among the four studies which evaluated more than 70 autistic males, the percentage who expressed the fragile site ranged from 1 to 16%. The reasons for such a discrepancy may be due to methodologic differences among the studies (e.g., different culture techniques, varying thresholds for making an autistic diagnosis, and varying degrees of sampling bias), or to inherent variability of the syndrome itself.

These findings are intriguing since they suggest a link between genetic vulnerability and biologic forms of psychopathology. The fragile X syndrome, in fact, represents a particularly good model for the study of such a relationship, since the genetic lesion responsible for the syndrome is fairly well-circumscribed (although poorly understood), yet associated with genetic and phenotypic heterogeneity both within and across families. Greater understand-

ing of the basis for such heterogeneity carries with it the potential for identifying salient risk factors involved in the development of specific psychiatric disorders.

The aim of this study is to characterize the range of psychopathology manifested by the 14 boys and young men with fragile X syndrome who were followed in our research program. We were particularly interested in exploring the specific character of the reported social and attentional difficulties of fragile X males.

METHOD

Subjects

The present study included 14 males with fragile X syndrome, referred to the Yale Child Study Center for extensive physical, cognitive, adaptive, language, and behavioral assessments. Referrals originated from physicians at two university-based departments of human genetics who are familiar with our investigations. Cytogenetic testing for fragile X syndrome had been undertaken in 11 of the cases because of the presence of developmental delays within the context of a family history of mental retardation. Testing was conducted in the three other cases as part of a thorough work-up to identify medical causes of mental retardation. In one case from each of these two groups, physical features consistent with the fragile X phenotype were identified prior to cytogenetic testing, however, in no case were suspicions of fragile X raised because of the presence of particular social or behavioral attributes. Twelve of the subjects were tested in the Human Genetics Department of Yale University School of medicine, using folate-deficient medium 199 with 2% fetal calf serum (Lubs, Watson, Breg, & Lujan, 1984). The remaining two subjects were tested in another regional university-affiliated department of human genetics also using folate-deficient media. Cytogenetic diagnoses were considered reliable in all cases. The percentage of cells which demonstrated the fragile X site ranged from 4 to 66% across the 14 subjects (see Table I), a range consistent with those reported in the literature. Subjects with a fragility below 10% had first-degree relatives with convincing cytogenetic findings (fragility above 17%). In addition, DNA typing was performed in several pedigrees in which the pattern of inheritance was unclear. Referrals to our research program were based solely on the diagnosis of fragile X syndrome, without regard to the presence or absence of psychopathology. As depicted in Table I, the subjects ranged in age from 3 to 27 years and exhibited a broad range of cognitive ability (from normal intelligence to moderate mental retardation). Adaptive functioning, as assessed by the revised Vineland Adaptive Behavioral Scales (Sparrow, Balla, & Cicchetti,

Table I. Subject Characteristics[a]

S	CA	MA	IQ	ABC	ABC/MA	SOC/MA	IP/MA	MAL	ADD	PDD	ANX	Other %	F(X)
1	3-8	2-3	51	1-9	78	70	67	SIG	+	–	–	–	22
2	4-11	4-5	80	4-1	92	83	100	SIG	+	–	–	OPP	14
3	6-3	3-3	44	3-9	115	123	126	INT	+	[b]	–	–	34
4	7-0	6-4	85	4-6	71	80	90	INT	+	–	–	OPP	41
5[c]	7-9	5-5	66	4-9	88	85	89	INT	+	–	–	–	14
6	10-8	5-4	52	6-3	117	77	91	INT	+	–	+	AVOID	21
7	12-4	5-0	45	5-3	105	80	88	SIG	+	–	–	–	33
8	14-11	5-10	44	6-3	107	69	70	SIG	+	–	+	–	4
9	15-3	6-7	48	5-8	86	72	86	INT	+	–	+	OPP	10
10	15-11	5-8	38	6-4	112	119	123	INT	+	[b]	–	AVOID	25
11[d]	16-0	4-4	30	4-6	104	60	50	SIG	–	+	–	–	8
12	25-3	7-4	53	9-4	127	143	95	INT	+	–	–	TS	38
13	27-3	6-3	46	4-9	76	82	91	SIG	+	–	+	–	14
14	27-9	6-1	49	4-1	67	63	93	SIG	+	–	–	–	15
Mean			52		96	86	90						
SD			±14		±18	±24	±19						

[a]CA = chronological age; MA = mental age (Stanford-Binet); ABC = Adaptive Behavior Composite on VABS; ABC/MA = ABC of VABS/MA × 100; SOC/MA = socialization age equivalent on VABS/MA × 100; IP/MA = interpersonal age equivalent on VABS/MA × 100; MAL = maladaptive behavior section of VABS (SIG = significant; INT = intermediate as based upon normative data for nonintellectually impaired subjects of equivalent CA); ADD = attention deficit disorder; PDD = pervasive developmental disorder; ANX = anxiety disorder (overanxious or generalized anxiety disorder); OPP = oppositional disorder; AVOID = avoidant disorder; TS = Tourette's disorder; % F(X) = % of cells exhibiting the Fragile X site on cytogenetic screening.

[b]Met criteria for PDD diagnosis only transiently, early in life.

[c]One nonautistic subject received low scores within the socialization domain during the initial assessment. However, several follow-up assessments failed to reveal socialization deficits. It was suspected that strongly negative parental attitudes regarding the child (most prominent during the initial stages of referral) biased the first Vineland interview. Therefore, a subsequent administration of the VABS was used for analysis.

[d]This subject also met criteria for ADD, however, his symptomatology was judged to be secondary to infantile autism.

1984) was generally consistent with intellectual ability. All the subjects were outpatients, residing either with their families or in small group homes.

Procedure

The types and degree of psychopathology were determined by thorough developmental histories and direct neuropsychiatric examinations. The sources of information included parental interviews (focusing on developmental and psychosocial history), reports of medical, psychoeducational, and developmental assessments conducted over the years, extensive special education reports, and standardized parent and teacher questionnaires including the Connors Parent and Teacher Questionnaires (Goyette, Connors, & Ulrich, 1978), the Child Behavior Checklist (Achenbach, 1978), and the Autism Behavior Checklist, (Krug, Arick, & Almond, 1980), and the Fragile X List (R. Hagerman and T. Jackson, personal communication, November 1984). In addition, individual psychiatric interviews were conducted longitudinally with each subject and his family or caretakers by the authors. Supplemental data were provided through cognitive and language assessments conducted by members of our research group (Paul et al., 1987; Dykens, Leckman, Paul, & Watson, 1988). Final diagnostic fomulations were made on the basis of all available information by an experienced child and adolescent psychiatrist (J.D.B.) according to DSM-III criteria. Rating sheets listing each DSM-III criterion were used to summarize the data. The records of four subjects were randomly selected for assessment of interrater reliability, conducted independently by a second experienced child and adolescent psychiatrist (J.F.L.). When DSM-III criteria were applied, 100% agreement was obtained on these four cases.

RESULTS

Neuropsychiatric Disorders

All 14 patients exhibited emotional and behavioral symptoms of a severity warranting clinical psychiatric diagnosis. As depicted in Table II, a range of psychiatric disorders were present, with attention deficit disorders and anxiety disorders predominanting. The signs and symptoms exhibited by the subjects were readily identifiable and were similar in kind to those observed among children and young adults without developmental disorders (with the possible exception of persistent gaze aversion among the socially engaged subjects). No unique neuropsychiatric symptoms were noted among the study subjects. In addition, it was possible to apply DSM-III criteria without significant difficulty.

Table II. Psychiatric Diagnoses Among 14 Fragile X Subjects[a]

Disorder	No. affected	% affected[b]
Pervasive developmental disorders		
Infantile autism	1	7
Other PDD	0	0
Attention deficit disorder		
With hyperactivity (ADDH)	10	71
Residual state (ADD-R)	3	21
Total ADD disorders[c]	13	93
Anxiety disorders		
Overanxious or generalized	4	29
Avoidant disorder	2	14
Oppositional disorder	3	21
Tourette's disorder (TS)	1	7

[a]Based on DSM-III criteria.
[b]Several subjects met criteria for more than one disorder.
[c]The 14th subject also met criteria for ADD, however, his symptomatology was judged to be secondary to infantile autism.

Attention Deficit Disorders

As depicted in Table III, all 14 subjects manifested clear indications of inattention and hyperactivity, and 13 of the 14 manifested clinically significant degrees of impulsivity. These behavioral characteristics were, for the most part, pervasive and not confined to specific environmental situations (as is often the case for nonretarded individuals with disorders of attention). The Vineland Adaptive Behavior Scales (VABS) provided one standardized source of data regarding ADD symptomatology (Dykens, Hodapp, & Leck-

Table III. Attention Deficit Disorders Among 14 Fragile X Subjects[a]

Symptom (lifetime)	No. affected	% affected
Inattention	14	100
Impulsivity	13	93
Hyperactivity	13	93
Onset before 7 years	14	100
Absence of schizophrenia, affective disorder, and severe or profound mental retardation	14	100
Attention deficit disorder[b]		
ADDH	10	71
ADD-R	3	21

[a]Based on DSM-III criteria.
[b]The 14th subject also met criteria for ADD, however, his symptomatology was judged to be secondary to infantile autism.

man, submitted). Prominent signs of inattention, impulsivity, and hyperactivity were identified among 10 (71%) of the subjects during Vineland interviews with primary care-givers. Connors Parent and Teacher Questionnaires were available for 7 of the 13 subjects who met diagnostic criteria for ADD. The scores for all 7 subjects met or exceeded a value 2 standard deviations above the mean for a normative sample of children of equivalent mental age (Goyette et al., 1978). Diagnostically, 13 of the 14 subjects met DSM-III criteria for an attention deficit disorder, 71% for ADDH, and 21% for a residual syndrome. (The 14th subject also met criteria for ADD, however, his symptomatology may have been secondary to infantile autism.)

Anxiety Disorders

Findings regarding the presence of symptoms of anxiety confirmed our clinical impressions. The fragile X subjects regularly presented with significant degrees of expressed anxiety, including persistent worry regarding competence, performance, and social acceptability, apprehension of future events, marked self-consciousness, and somatic complaints without physical basis. Four subjects (29%) met criteria for overanxious or generalized anxiety disorders, and 2 (14%) met criteria for avoidant disorder (one of whom also received an overanxious disorder diagnosis).

Autistic Disorders

For the present study, three groups of autistic symptoms were considered, including social dysfunction, communication deficits, and behavioral abnormalities (Rutter, 1978). As can be appreciated from Table IV, only three of the subjects manifested significant deficits in their capacity for empathy and social responsivity at some time in their lives. In two of the three, these deficits were transient, resolving by age 3 years. The other subjects were generally described by parents and teachers as consistently affectionate, engaging, and sensitive to the feelings of family members and peers. These views were consistent with the clinical impressions of the investigators. Although four of the subjects exhibited developmentally inadequate degrees of participation in peer group activities, only one demonstrated a lack of interest in social relationships. The other three subjects experienced a significant degree of social anxiety which interfered with their desires for peer acceptance and affiliation.

Social functioning was assessed more formally through administration of the VABS. In general, the fragile X subjects demonstrated adaptive social functioning which was consistent with their overall cognitive ability. This

Table IV. Infantile Autism Among 14 Fragile X Subjects[a]

Symptom	No. affected	% affected
Onset before 30 months	14	100
Pervasive lack of responsiveness to other people		
Persistent	1	7
Transient	2	14
Poor eye contact	7	50
Inadequate peer relationships or social activity	4	29
Inadequate or inappropriate affection seeking	0	0
Gross deficits in language development	7	50
Peculiar speech patterns	9	64
Abnormalities in speech form and content (e.g., echolalia, metaphorical language, pronomial reversal)	9	64
Abnormal speech production (e.g., intonation, rhythm)	3	21
Bizarre responses to various aspects of the environment	9	64
Stereotypy and/or self-injurious behavior (lifetime)	9	64
Perseverative interests and preoccupations	3	21
Insistence upon sameness in environment and routines	2	14
Preoccupation with part-objects, unusual attachmnets	2	14
Absence of hallucinations, delusions, loosening of associations, and incoherence as in schizophrenia	14	100
Infantile autism	1	7
Transient autistic features	2	14

[a]Based on DSM-III criteria.

is reflected in the ratios of socialization age/MA and interpersonal age/MA. The group means for these ratios were 0.86 and 0.90, respectively.

Abnormalities in language and communication functioning were particularly prevalent among our subjects, often those commonly associated with autism. Frequent findings included the presence of echolalia, verbal perseveration, idiosyncratic responses, and abnormalities in the intonation and rhythm of speech. In addition, gaze aversion, a behavioral symptom often closely linked to autism was present among one-half of the subjects, including those described as socially responsive and affectionate (see Table IV).

Similar findings were noted in relation to behavioral functioning. More than half of the subjects exhibited stereotypic and/or self-injurious behavior

and nearly one-quarter demonstrated perseverative preoccupations and interests. Other atypicalities of behavior were experienced by several patients (see Table IV).

For some subjects, the symptoms of social anxiety, language abnormality, and stereotypic behavior tended to cluster. Three of the four subjects with anxiety disorders also exhibited language abnormalities and stereotypic behaviors. Five other subjects manifested both language abnormalities and stereotypy. Among the remaining subjects, however, symptoms were distributed randomly.

Despite the frequent occurrence of autistic-like language and behavioral attributes among the fragile X subjects, only one met full diagnostic criteria for a pervasive developmental disorder, whereas two others met such criteria only transiently quite early in life (see Table IV). Although the majority of subjects exhibited poor eye contact, atypical speech and language functioning, and stereotyped behavior, only one experienced social dysfunction of a severity sufficient for an autistic diagnosis.

Standardized ratings supported these diagnostic conclusions. The parents of eight subjects completed the Autism Behavior Checklist (Krug et al., 1980). Scores for seven of these subjects fell in the probably not autistic range while those for the eighth fell in the possibly autistic range. (The latter subject received the diagnoses of attention deficit disorder, residual type and Tourette's disorder. The subject who met DSM-III criteria for autism recieved a score of 47, falling in the probably not autistic range.)

DISCUSSION

During the past decade, the fragile X syndrome has become recognized as a significant cause of cognitive impairment and behavioral disturbance within the mentally retarded population. The present findings support those of the available literature in revealing a very high prevalence of psychiatric disorder, particularly of attention deficit disorder. Thirteen of the 14 subjects manifested behavioral signs clearly indicative of attention deficit disorder, even when developmental factors were considered. Although oppositional features were also present among three of these subjects, and symptoms of anxiety among four, autistic social dysfunction was notably absent. This impressive frequency of ADD symptomatology far exceeds the estimates of attentional disorders among the general mentally retarded population (approximately 15%), suggesting possible specificity of such disorders among the referred fragile X population. These findings also support the view that judicious behavioral and pharmacological interventions focused on this problem may significantly improve the functional capacity of many fragile X individuals.

Our results, however, are at variance with those of several groups of investigators who report a particularly high frequency of autism among their fragile X subjects. (In the present study, only one subject met diagnostic criteria for autism, and two others met criteria only transiently quite early in life.) Differing diagnostic interpretations of gaze aversion and social avoidance may underlie this discrepancy. Although these symptoms may represent manifestations of autistic social dysfunction, they may also reflect the presence of underlying social anxiety. The latter interpretation more adequately reflects the psychological status of our subjects who regularly demonstrated the capacity to form reciprocal, empathic relationships, yet frequently manifested symptoms of anxiety. In fact, clearly one-third of the subjects exhibited sufficient symptomatology to qualify for a diagnosis of anxiety disorder (overanxious, generalized, or avoidant). It is likely, therefore, that the social difficulties so common among our subjects reflect a significant degree of social anxiety rather than of autistic detachment. This hypothesis is supported by data from the VABS, a measure that is sensitive to the social deficits present among autistic individuals and capable of differentiating autistic from nonautistic, mentally retarded and atypical children (Volkmar et al., 1987). As previously reported (Dykens et al., 1988), the fragile X subjects did not demonstrate deficits in socialization relative to other aspects of adaptive functioning. The social functioning of the fragile X subjects (as assessed by the socialization domain of the VABS) was generally consistent with overall developmental ability (mean socialization age equivalent/MA = 0.86 and mean interpersonal age equivalent/MA = 0.90; see Table I). This contrasts with findings for autistic individuals, who manifest significant socialization deficits on the VABS, typically receiving socialization and interpersonal age/MA ratios of approximately 0.50 (Volkmar et al., 1987). It should be noted, however, that the one subject who met diagnostic criteria for autism, did have the lowest scores on the VABS socialization domain, and these scores were quite similar to those received by autistic individuals (socialization age/MA of 60 and interpersonal age/MA of 50).

These findings raise provocative questions regarding the pattern of psychiatric symptoms exhibited by individuals with fragile X syndrome. Further investigations are necessary to determine whether the language, behavioral, and social gaze disturbances experienced by these patients are indicative of an autistic disorder, an anxiety disorder, or a unique neuropsychiatric syndrome specific to fragile X syndrome.

The present paper raises another important issue, namely, the syndrome's potential contribution to our understanding of the etiologic factors that underlie specific forms of developmental and neuropsychiatric disturbance. In this regard, several characteristics of the fragile X syndrome are of particular significance. First, the fragile X is the only known fragile site

associated with an identifiable clinical phenotype, suggesting that either chromosomal location or unique molecular attributes of the fragile X site itself may play an etiologic role in the development of associated developmental and psychiatric abnormalities. Second, the physical, cognitive, and behavioral phenotype occurs with appreciable variability within and across families, suggesting the influence of genetic and/or psychosocial factors that serve to modify clinical expression. In view of these observations, there exists the potential for significant advances in our knowledge of abnormal cognitive and behavioral functioning through further study of individuals with fragile X syndrome.

The findings of the study should be regarded as preliminary, however, in view of the small sample and potential problems regarding the method of subject ascertainment. The subjects discussed in the present paper were referred for cytogenetic testing either because of a family history of mental retardation or as part of a thorough evaluation to rule out potential biologic causes of cognitive impairment (in the absence of a positive family history). Although 2 of the 14 subjects were noted to have some physical features suggestive of the syndrome prior to testing, none of the subjects were tested because of the presence of a particular cognitive, language, or behavioral phenotype. Referrals to our research group were made on the basis of the cytogenetic findings alone, rather than on the basis of specific physical or behavioral attributes. Finally, the demographic features of our subjects are similar to those of larger outpatient groups reported in the literature (Brown et al., 1986; Hagerman et al., 1986; Levitas et al., 1983), suggesting that our sample may be typical of fragile X groups identified by other investigators. Nevertheless, given the circumstances of subject identification, it is still possible that the presence of certain phenotypic characteristics led families, agencies, and physicians to refer patients for genetic testing. Further work may need to focus on representative samples identified by unbiased methods of screening random samples of mentally retarded individuals from all available sources.

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