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Correlation of Family History with Specific Autistic Subgroups: Asperger's Syndrome and Bipolar Affective Disease[1]

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The etiology of infantile autism is not known. To assess the possible role of familial psychopathology, we investigated a group of autistic subjects subgrouped by level of language function. Family histories were obtained by the family history method. Neurological status was assessed by neurological diagnostic examination and prenatal and perinatal history. The results showed a high incidence of Asperger's syndrome in family members of high-functioning autistic subjects only. The rate of bipolar affective disorder in family members was 4.2%, higher than in the general population; it was significantly higher in families with Asperger's syndrome, suggesting an etiological link between Asperger's syndrome and manic depression. Positive neurological findings were concentrated in the low-functioning subgroup. These findings imply different etiologies for high- versus low-functioning autism, with high-functioning autism related to familial factors, especially Asperger's syndrome.

Genetic factors, including familial psychopathology, have been implicated in the etiology of infantile autism. This issue, however, is complicated by the heterogeneity of autistic syndromes. It seems possible that familial psy-

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chopathology may be relevant to the etiology of some specific subgroups of autism. With this in mind we have undertaken a family history study of a wide spectrum of autistic subjects to determine whether family history correlates with identifiable subgroups of autism.

A family study of autism by Herzberg (1976) showed that families of autistic subjects have more schizophrenia, manic depression, and attempted suicides than controls. More recently Komoto, Usui, and Hiratu (1984) presented three case studies of autistic children who also had affective disorder and suspected family histories of depression and manic depression. Gillberg (1985) presented a case of Asperger's syndrome with cycloid manic-depressive features and a family history of manic depression; he emphasized the clinical similarities between Asperger's syndrome and autism. DeLong and Aldershof (1983) found high rates of manic depression in the families of children with autism or pervasive developmental disorder with special abilities.

Many authors have urged the need for subgrouping of autism, but no generally accepted categorization of subgroups has emerged. The level of intelligence is obviously a crucial factor in the prognosis of autism (Eisenberg, 1956) and low intelligence correlates with electroencephalographic abnormalities and gross neuropathology (Rutter, 1983). The risk of autism increases with lower IQ (Rutter, 1983; Wing & Gould, 1979). However, there have been no clear indications of different etiologies corresponding to the level of functioning.

In the present paper, we asked the following questions: (1) Does the incidence of familial psychopathology (including developmental disorders and mental retardation) differ in the families of our autistic probands from that found in the general population? (b) Are specific forms of familial psychopathology overrepresented in the families of the probands? and (c) Does family history correlate with any identifiable subgroup of autism, in particular with high- versus low-function?

METHODS

We evaluated 51 individuals, 42 male and 9 female, ranging in age from 3.0 to 35 years (mean 13 $\pm$ 7 years), with diagnoses of autism or pervasive developmental disorder diagnosed by a child neurologist, psychiatrist, or psychologist. Individuals participated as part of ongoing studies of developmental disorders involving several medical centers including the Massachusetts General Hospital and the Boston University School of Medicine and the Child Neurology Society/International Neuropsychological Society Task Force, Nosology: Higher Cortical Function Disorders in Children. Subjects came from pediatric neurological practice, from special schools or classes for children with autism or pervasive developmental disorders, or through lay family organizations. The sample represented the full spectrum of autism and

autistic-like disorders, with intellectual levels ranging from normal to severely retarded. Diagnoses were made using DSM-III (American Psychiatric Association, 1980).

We believe the sample is representative of the autistic spectrum, with one possible exception: Our sample was drawn disproportionately from the higher socioeconomic classes; 71% were from Classes I–II, and only 29% from Classes from III–IV.

Information was obtained for each proband and family from a structured comprehensive interview with one or both parents. Developmental history, including prenatal and perinatal events, was collected using a systematic questionnaire. Forty-seven (92%) of all subjects had undergone comprehensive neurological evaluations. Medical and neurological records were reviewed including electroencephalogram (EEG), computerized tomography (CT scan), or pneumoencephalogram (PEG), where available. Family neuropsychiatric history was recorded according to the Family History Research Diagnostic Criteria (FH-RDC; Andreasen et al., 1977), which is consistent with DSM-III. The family history interviewer had limited information on each proband prior to the interview. Data were obtained, as far as possible, on all first- and second-degree relatives of the probands. Rates of illness/disorder were recorded as uncorrected percentages. Socioeconomic status (SES) was estimated for each proband's family using the education and occupation factors of the Hollingshead scale (1975). Cognitive ability was determined from the most recent neuropsychological assessment for each individual. We subgrouped the probands according to the level of language function. We arbitrarily defined a high-functioning group as those with a verbal IQ $\geq$ 70. Verbal IQ correlates with outcome favorability and functional intelligence (Eisenberg, 1956).

Asperger's syndrome for family members was defined according to the clinical description of Wing (1981): abnormal content and prosody of speech; abnormal nonverbal communication (intonation of speech, expression, and gestures); impairment of two-way social interaction and inability to understand and use rules of social behavior; repetitive activities and resistance to change; clumsy gross motor coordination; excellent rote memory; intense interest in one or two arcane or abstruse subjects; special abilities as in music or chess; and eccentricity and exclusive attention to one's own interests.

Intercorrelations for subgroups were determined by chi-square analysis.

RESULTS

Characteristics of Probands

Table I describes 51 probands. Forty-two (82%) were male. Thirty-six (70%) were below age 15. Data for level of functioning were available on

Table I. Characteristics of Probands

Level of functioning (N = 44)	n	%		
IQ < 50	18	41		
IQ 50-69	7	16		
IQ ≥ 70	19	43		
Neurological risk factors			No. affected	Total %
Prenatal or perinatal complications			25/47	53
Identifiable brain damage (EEG, CT, PET, PEG)			22/51	43

44 of 51 (86%) of the probands. Of these, 18 had a measured verbal intelligence quotient of less than 50, 7 between 50 and 69, and 19 greater than 70 (Table I). The number of females for whom we had cognitive information is small (7/44, 16%); they displayed a significantly lower level of functioning than males, $\chi^2 = 6.93$, $p < .01$. Six of the seven females, but only 33% of males, had an IQ less than 50.

Indications of neurological pathology on the basis of an abnormal EEG, CT scan, PEG, or neurological examination were found in 25 of 47 probands for whom this information was available. Neurological abnormality correlated with a low level of cognitive functioning, $\chi^2 = 7.33$, $p < .01$. Fourteen of 18 (78%) who had an IQ less than 50 had positive neurological findings. Of the 23 probands who had an IQ greater than 50 only 8 (35%) had identifiable brain damage.

Parental or perinatal complications were identified in 22 (43%) of the entire group, but did not correlate with low function nor with neurological abnormality. Of the 21 for whom we also had neurologic information, 14 (67%) had abnormal neurological findings (ns). Of 18 individuals who had an IQ less than 50, 9 (50%) had evidence of prenatal or perinatal complications, and of subjects who had an IQ greater than 50, 11/26 (42%) had prenatal or perinatal complications (ns).

Family History

Table II shows the rates of psychopathology and cognitive disorders among 929 first- and second-degree relatives of our 51 probands. Of the 51 probands, 23 had a family member with manic depression. The overall incidence rate of manic depression is 4.2% (39/929) and of major depression is 8.0% (74/929). Schizophrenia was found in only 0.4% (4/929), alcoholism in 6.5% (60/929), and anxiety disorders in 10.0% (93/929). A diagnosis of autism occurred in only three relatives, all second-degree (0.3% of total sam-

Table II. Incidence of Psychopathology Among First- and Second-Degree Relatives of 51 Autistic Spectrum Probands

		Manic depression		Major depression		Schizophrenia		Alcoholism		Autism		Asperger's syndrome		Language delays		Stuttering		Mental retardation		Anxiety disorders	
Relatives	*N*	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Male	486	20	4	34	7	1	0.2	42	9	3	0.6	17	4	23	5	10	2	6	1	37	8
Female	443	19	4	40	9	3	0.6	18	4	0	0	0	0	12	3	3	0.6	1	0.2	56	13
Maternal	438	22	5	42	10	3	0.6	30	7	1	0.2	6	1	15	3	4	0.9	3	0.6	50	11
Paternal	401	13	3	27	7	1	0.2	29	7	2	0.4	6	1	9	2	7	2	3	0.7	31	8
Siblings	90	4	4	5	5	0	0	1	1	0	0	5	5	11	12	2	2	0	0	12	13
First-degree	196	10	5	16	2	1	0.5	5	3	0	0	9	5	15	8	7	4	1	0.5	31	16
Second-degree	733	29	4	58	8	3	0.4	55	8	3	0.4	8	1	20	3	6	0.8	6	0.8	62	8
Total	929	39	4	74	8	4	0.4	60	6	3	0.3	17	2	35	4	13	1	7	0.7	93	10
No. of families	51	23	45	35	69	4	8	28	55	3	6	15	29	13	25	13	25	7	14	18	35

ple). Speech disorders, primarily stammering, occurred in 1.4% (13/929). Mental retardation was found in 0.7% (7/929).

Seventeen relatives in 15 families had findings permitting a diagnosis of Asperger's syndrome. Thirteen of the 19 probands (68%) with an IQ greater than 70 had a positive family history of Asperger's syndrome in at least one first- or second-degree relative. In contrast, of those probands with an IQ less than 70, only two had a family history of Asperger's syndrome. This difference is highly significant, $\chi^2 = 17.56, p < .001$. The incidence of manic depression in families positive for Asperger's syndrome is 6.1% (19/314) compared to 3.3% (20/615) for families negative for Asperger's syndrome, $\chi^2 = 4.04, p < .05$.

The incidence of manic depression in the families of all high-functioning probands (those with IQ > 70) is 5.0% (19/376), compared to a rate of 3.7% (17/463) in the families of low-functioning probands (ns).

DISCUSSION

This study finds that a large proportion of high-functioning individuals within the autistic spectrum have a positive family history for an autistic-like personality disorder (Asperger's syndrome), whereas low-functioning autistic subjects have a very low incidence of Asperger's syndrome or other autistic-like disorders in their family history. In contrast, low-functioning autistics have a high incidence of abnormal neurological findings on EEG or CT scan, whereas high-functioning individuals have a much lower incidence.

These findings suggest that high- and low-functioning autism are, in general, different conditions. According to this formulation, high-functioning autism is generally a familial condition (or at least has a strong familial factor) related to Asperger's syndrome, and low-functioning autism has a much larger factor of neurological damage, without strong familial factors relating to Asperger's syndrome. Of course, both factors presumably interact in some cases.

We may ask whether our high-functioning probands, particularly those with a family history of Asperger's syndrome, may themselves be diagnosable as Asperger's syndrome. Applying the criteria of Szatmari (1986), we found 15 of the 19 probands in the high-functioning subgroup fit that diagnosis (unpublished data). This suggests that high-functioning autism and Asperger's syndrome are in large part equivalent and have a predominantly familial etiology.

The second major point to emerge from this study is the high incidence of manic depression in the families of these autistic probands. This incidence is 4.2%, about fivefold greater than that expected in the general population

according to published data (Robins et al., 1984). There have been suggestions that the incidence of manic depression may be higher in higher socioeconomic classes (Klerman, 1981). Because these classes are overrepresented in our sample, we compared the rate of illness between higher (I and II) and lower (III, IV, and V) socioeconomic levels. The rate is 4.0% in classes I and II and 5.0% in classes III, IV, and V. The fact that these rates are nearly equal across socioeconomic classes in our sample makes it unlikely that SES can explain the higher incidence of manic depression in our sample as compared to published data for the general population. It is noteworthy that the incidence of unipolar depression (8.0%) is not higher than that expected for the general population (Robins et al., 1984). Using the same methods and criteria, we previously studied the families of manic-depressive children and found that the incidence of both bipolar (13%) and unipolar depression (27%) were significantly increased (Dwyer & Delong, 1987). The increase in bipolar disease without a concomitant increase in unipolar disease thus seems to be peculiar to the present sample and is unexplained.

The contribution of this increased incidence of manic depression to the etiology of autism in our sample is unclear. Its incidence is increased compared to the general population in the families of both high- and low-functioning autistic children. The incidence tends to be higher in the families of high-functioning than of low-functioning autistic children and is significantly higher in the families with Asperger's syndrome. These findings suggest a possible etiologic link between familial bipolar disease and high-functioning autism, or more specifically Asperger's syndrome. Such a link has been suggested previously by the anecdotal case reports described in the Introduction. Perhaps the strongest argument for a link between Asperger's syndrome and manic depression is found in the work of Wing (1981) who followed a series of individuals with Asperger's syndrome through puberty. Of these, 23% showed signs of affective illness, 11% had attempted suicide, and 17% were psychotic (with delusions/hallucinations, catatonic stupor, or "schizophrenia"). Since suicide and adolescent catatonia may be manifestations of affective disease (especially bipolar), nearly half of the individuals in Wing's series presumably developed overt severe affective disorder. She did not present family history data.

Certain methodologic aspects of this study should be mentioned. It was not possible to carry out the study in formal blinded fashion. However, neither the person taking the family history nor the familial informant knew which subgroup the probands might fall into, since the assignment to subgroups was done only after the family history data were gathered. Also, the assignment to subgroups was done entirely independently of the family history data. Because of the independent collection and the complexity of the medical and psychometric assessments it is unlikely that observer bias influenced the results. The initial implicit hypothesis was that familial affec-

tive disease was associated with autism, or more specifically, with some subgroup of autism. The finding of Asperger's syndrome in families and its very strong correlation with high function in probands was entirely unanticipated, as was the correlation between Asperger's syndrome and bipolar disease in families.

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