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Implication of Sex Differences in the Familial Transmission of Infantile Autism[1]

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There are studies suggesting possible hereditary influence in autism. Data on 102 autistic children, 78 boys and 24 girls, showed that there was a significantly greater proportion of autistic girls than boys with IQs less than 50 and with evidence of brain damage. The autistic girls also had a greater proportion of relatives affected with autism or cognitive-language deficit than did the boys. The implication of sex differences in the possible mode of familial transmission of autism is discussed.

One of the most overlooked features about infantile autism is the unvarying preponderance of male children who are affected with the disorder. Ratios from three to four boys to one girl have consistently been reported in the literature (Lotter, 1966; Rutter & Lockyer, 1967; Ritvo, Cantwell, Johnson, Clements, Benbrook, Slagle, Kelley, & Ritz, 1971; DeMyer, Barton, DeMyer, Norton, Allen, & Steele, 1973; Spence, Simmons, Brown, & Wikler, 1973; Campbell, Hardesty, & Burdock, 1978; Schopler, Andrews, & Strupp, 1979; Wing & Gould, 1979). Interestingly, the significance that this sex difference has with respect to theories of etiology and pathogenesis has not been fully explored.

A shift toward consideration of organic factors as potential causes of autism has followed the growing recognition that many autistic children show symptoms of neurological impairment. Nevertheless, it is not clear whether genetic factors, alone or in combination with environ-

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mental factors, may or may not contribute to the etiology of infantile autism. There are positive findings from family history studies that do suggest possible hereditary influence. So far the best estimate indicates that about 2% of the siblings of autistic children suffer from the same condition (Rutter, 1967). When this estimated sibling incidence is compared with the general population risk of 4.5 per 10,000 (Lotter, 1966), the rate of autism in siblings is 50 times higher. Furthermore, since the constellation of symptoms that are included within the diagnosis of autism represents a complicated structure of many variables, Folstein and Rutter (1977) have raised the possibility that it is not autism as such that is inherited, but rather that the genetic influence concerns a pervasive cognitive deficit of which autism is one part. Based on such a hypothesis, in a study of 21 same-sex twin pairs, they found that 9 of the 11 (82%) monozygotic twin pairs were concordant for at least one criterion for cognitive-linguistic impairments, whereas in only 1 of the 10 (10%) dizygotic twin pairs were the cognitive impairments present in both individuals. They concluded that there were important hereditary influences concerning a cognitive deficit that included but was not restricted to autism. On the other hand, based on the findings of both family and twin studies, Spence (1976) suggested that the nature of the causal mechanism could not involve either chromosomal anomalies or single gene effects but would most likely involve a complex genetic mechanism such as polygenic or multifactorial inheritance. The multifactorial model assumes that all genetic and environmental factors relevant to the etiology may be combined into a normally distributed underlying variable called liability. Everyone has some liability, however small, but only those individuals whose liability passes beyond a certain critical value called the threshold may be affected. The threshold can be located by equating the prevalence of persons affected and the proportional areas of the normal curve above the threshold. Under the multifactorial model, individuals of the less frequently affected sex are expected to be more severely ill, to have more affected relatives with any form of the condition, and to have a greater proportion of more severely affected relatives (Falconer, 1965; Reich, James, & Morris, 1972; Reich, Cloninger, & Guze, 1975). With multifactorial inheritance, it is possible to account for the small recurrence risk in families and the different rate in the two sexes.

The method of analysis to be presented here is based on Folstein and Rutter's hypothesis and the principles of multifactorial inheritance. The results reported in this study represent some initial data concerning the relatinship between sex differences and severity of illness in autism. Although some family data on the recurrence risk of autism are reported, they must be considered only preliminary. In a future paper, we plan to report the results of more rigorous testing of the multifactorial model utilizing family

data on specific measured variables that explore the possibility of a milder form of autism in the relatives of affected children.

METHOD

Subjects

From June 1974 to December 1979, 102 children (78 boys and 24 girls) were diagnosed as having infantile autism by at least two child psychiatrists and admitted to the autism program at the University of Iowa Child Psychiatry Service. All of the cases met the diagnostic criteria for autism outlined by Kanner (1943) and further delineated by Rutter (1971, 1977), namely, a serious impairment in the development of social relationships; delayed and deviant language development; stereotyped, repetitive, or ritualistic play and interest; and onset before age 3.

Data Collection

These children were evaluated on a ward for a period of 6 to 8 weeks. Data on each child'a psychiatric status and family history of social, cognitive, and language impairment were collected by interviewing the parents and by the use of questionnaires. Each child was routinely given a battery of psychological, educational, and language tests, and a neurological examination. Eighty of the children had an electroencephalogram. All case records of the 102 children were reviewed and pertinent data abstracted.

Data Analysis

The boys and girls were compared on each variable by using the chi-square test on qualitative data and the student's t statistic on quantitative measures.

RESULTS

Demographic Data

The mean age for the whole group was 6 years 7 months; the range was from 3 years 3 months to 20 years 4 months. There was no difference

between groups in the mean age (mean age, boys = 6 years 10 months; girls = 6 years 6 months). The male to female ratio was 3.25 to 1.

While more autistic girls than boys were firstborn (62% vs. 52%), there was a significantly greater proportion of only children among the girls (29%) than among the boys (11%) ($\chi^2 = 4.45$, $p < .05$). It follows that the girls tended to come from somewhat smaller families than the boys.

In both groups, the distribution of social class, judged by the occupation and education of the head of the household on the Hollingshead-Redlich Two-Factor Index (I as upper class, V as dependent, Hollingshead & Redlich, 1958) (mean social class for boys: 3.27 ± .85; girls = 3.29 ± 1.04), resembled that found in the general population of the state of Iowa, from which these children were taken, but there was a significantly greater proportion of social class IV in both groups than in the general population ($\chi^2 = 12.18$ for boys and $\chi^2 = 11.69$ for girls, both $p < .001$). This finding agrees with Schopler and Dalldorf's (1980) finding that most autistic children come from families in social class IV of the Hollingshead index and that autism is not a disease of the upper middle class.

Intelligence

Actual scores were available for all the girls and all but four boys (Table I). Even when those four untestable boys were assigned the worst score as required for their educational placement of severe mental retardation, i.e., IQ of 20, the mean IQ of total autistic boys (49.29 ± 21.94) was still higher than the mean IQ of girls. Furthermore, when we subdivided the sample into three categories—IQ less than 50, IQ 50-69, IQ greater than 70—we found that the boy-to-girl ratio in the higher IQ groups (IQ 70 or more) was higher than in the severely retarded group (IQ less than 50) by 4.7:1 versus 2.9:1. Our autistic girls seemed to have lower IQs than the boys, and by implication were more severely impaired.

Motility Disturbances

More than half of the autistic children (56%) had motor disturbances such as dystonia, abnormal posture and gait, dystonic posturing of hands and fingers, hand flapping, tremor, ticlike movement, ankle clonus, and emotional facial paralysis (i.e., asymmetry of the lower portion of the face when children smiled or spoke spontaneously). These are all signs of dysfunction in the basal ganglia, particularly the neostriatum, and closely related structures of the mesial aspect of the frontal lobe (Rylander, 1939; Martin, 1967; Schwab & England, 1968; Damasio & Maurer, 1978). Ab-

Table I. Comparisons of 78 Autistic Boys and 24 Autistic Girls on Selected Variables

Variables	Boys (N = 78)		Girls (N = 24)		t or χ^2	p
Mean IQ of those testable (*SD*)	50.47	(21.71)	45.54	(23.97)	t = .94	< .40
Enuresis (after age 3½ years)	46	(59%)	21	(86%)	χ^2 = 5.10	< .05
Encopresis (after age 3½ years)	51	(66%)	21	(86%)	χ^2 = 3.35	< .10
History of epilepsy	13	(17%)	10	(42%)	χ^2 = 6.57	< .02
Abnormal EEG[a]	10	(17%)	8	(38%)	χ^2 = 5.03	< .05
Evidence of brain damage	15	(19%)	13	(54%)	χ^2 = 8.93	< .01

[a]EEGs were done on 59 boys and 21 girls.

normal movements were somewhat more common among the autistic girls than the boys (67% vs. 53%).

Bladder and Bowel Control

Significantly more autistic girls than boys had not developed daytime bladder control by age 3½ (Table I). There was also a tendency for more girls than boys to fail to gain bowel control by age 3½. These findings suggest greater delay in or interference with brain maturation in girls than in boys; again, the probable site of the lesion is in the frontal lobe (Andrew & Nathan, 1964).

Epilepsy and Electroencephalogram

Twenty-three of the 102 children (23%) had developed epilepsy by the time they were admitted to the program; this was significantly more common among autistic girls (Table I).

Electroencephalograms were done on 78% of autistic boys and 88% of girls. There was a significantly greater proportion of girls' than boys' EEGs that were considered abnormal due to focal or diffuse spike, slow wave, or paroxysmal spike and wave patterns (Table I).

Brain Damage

We applied Rutter and Lockyer's (1967) criteria for brain damage to the present sample. In 28% of the total sample there was evidence of probable brain damage, the same proportion as that observed (29%) by Rutter and Lockyer in a study of 63 autistic children. Furthermore, we found that more autistic girls than boys met criteria for brain damage (Table I).

Severity of Cognitive and Neurological Impairment

When IQ less than 50 and evidence of brain damage were used as criteria for determining the severity of impairment, we found that there was a significantly greater proportion of autistic girls (7 cases, 29%) than boys (8 cases, 10%) that could be classified as severely affected ($\chi^2 = 5.23, p < .05$).

Cognitive-Language Deficit in Parents and Sibs

Two of the 102 children were siblings, brother and sister. Thus, 1 out of 31 full siblings (3%) of autistic girls and 1 out of 116 full siblings (1%) of autistic boys were affected with autism. If the diagnostic entity of autism was extended to included various speech and cognitive disability, as proposed by Folstein and Rutter (1977), then the incidence of this spectrum disorder of autism in the first-degree relatives of autistic girls (8%) was higher than in the relatives of boys (3%).

DISCUSSION

There are three striking findings in the present study. First, our autistic girls seemed to be more severely impaired in cognitive functions than boys; i.e., the girls had lower mean IQ than boys and there were more autistic girls than boys with IQs below 50. Second, there were significantly more autistic girls than boys who showed evidence of neurological impairment, i.e., failed to develop bladder control by age 3½, developed epilepsy before entering the program, had abnormal EEGs, and met criteria for brain damage. Finally, the autistic girls had more first-degree relatives affected with autism or autism spectrum disorder than did the autistic boys. The first two findings suggest that autistic girls are more severely impaired, i.e., more deviant in liability. The third finding suggests that the first-degree relatives of autistic girls have a higher "dose" of genes responsible.

There is general agreement among those who have reviewed the research that no known factors in the psychological environment of a child cause autism and that when etiology is eventually established, biological factors will be found to play a major role (Ornitz & Ritvo, 1976; Rutter, 1977; Schopler, 1978). Previous studies have shown that males are more susceptible than females to a wide variety of pre- and perinatal brain insults (Gruenberg, 1966; Taylor, 1969; Flor-Henry, 1974), central nervous system infections in childhood (Schlegel & Bellanti, 1969; Washburn,

Medearis, & Childs, 1965), and specific delays in development (Rutter, Tizard, & Whitmore, 1970). Therefore, it is reasonable to postulate that the sex difference in the prevalence of autism is due to biological factors causing the threshold to be more deviant in females; i.e., a higher dose of genes is needed to make a girl affected at all.

When IQ of 50 and criterion of brain-damaged described as above are used as objective, quantifiable means of determining the severity of the index cases in our present population, our study suggests that autistic girls are more severely affected than are boys. This hypothesis is supported by an epidemiological study conducted by Lotter (1966) reporting that all (100%) of the autistic girls (9 cases) had an IQ below 55, while 57% of the boys (13 out of 32 cases) did so. This hypothesis is further supported by Wing's (Note 1) observation that "on the whole, girls tend to be among the most severely handicapped."

The findings of the present study appear to suggest that if autism is inherited, the specific mechanism may involve multifactorial transmission. In order to test the applicability of the multifactorial model to observed data, it is necessary to have data on the prevalence of autism and/or cognitive disabilities in the relatives of a representative sample of cognitively disabled individuals. Our study design did not incorporate this feature, nor did it include data from different types of relatives, e.g., parents, cousins, grandparents. Moreover, in the statistical analysis of family data to determine the relative importance of genetic and environmental factors in the etiology and transmission, the affected relatives are divided into four groups: male relatives of male probands, male relatives of female probands, female relatives of male probands, and female relatives of female probands. Studies must therefore be large enough to describe the relationship among these four groups in a statistically significant manner. Since the population frequency of autism is very low, the rate in relatives of autistic individuals will also be low even in conditions with a high heritability (Smith, 1974; Curnow & Smith, 1975; Folstein & Rutter, 1977). No systematic family data about autism according to sex are available in the literature. One possible explanation is that the numbers of autistic girls included in most of the previous studies were relatively small. A collaborative, cross-national study of family history variables according to sex appears to be a logical next step toward clarifying the mode of inheritance of autism.

REFERENCE NOTE

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