FAMILY GENETIC STUDY OF CHILDHOOD AUTISM

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Summary :

There is considerable evidence from family and twin studies that aetiology of autism is predominantly genetic. However, the definition of the phenotype is questionable and it is suggested that the genetic liability for autism may be expressed in nonautistic relatives in a phenotype that is milder but qualitatively similar to the defining features of autism. This study was aimed to evaluate the rate of childhood autism and autism like features among the first degree relatives of austistic probands. Sixty five consecutive cases of childhood autism attended in Child Mental Health Outpatient Clinic of Bangabandhu Sheikh Mujib Medical University, Dhaka, from July 1998 to June 2000, satisfying clinical diagnosis of ICD-10 were included for this study. Same number of patients were selected as controls from children outpatient services of the University. A structured family history interview was used to assess the autism or autistic like features in first degree relatives of the probands of the both groups.

Though family history of childhood autism is insignificant, a considerable rate of social and communication impairments and restrictive & repetitive activities and interests were found in the first degree families of the autistic probands which are significantly higher than that of the families of the controls. Further studies are needed to establish the strengths of these autism phenotypic behavioural features and these should be included in the genetic analyses of childhood autism.

Introduction

Autism is a rare but severe developmental disorder characterized by lack of social relatedness, poor communication skills and absence of imaginative activity coupled with repetitive stereotypic behaviour and with early onset. Aetiology and pathogenesis of autism can view as a behavioural syndrome with various neurobiological causes with predominantly of genetic aetiology. It was estimated that about 47% of the autistic individuals had chromosome abnormalities and about half of whom showed the fragile X.[1] Another study showed the rate of fragile X in autism was about 2.5%.[2] The risk of recurrence of autism in families (i.e. the frequency of autism in subsequently born siblings) is estimated 6-8% or up to 200 times the risk in the general population.[3] Twin studies of geographically defined population[4-6] detected pairwise concordance rate ranged from 37-91 % between MZ twins and 0% in DZ twins, producing an average heritability estimate over 90%.

Although the importance of genetic factors in autism has been firmly established, the definition of the phenotype is questionable. A number of family and twin studies have suggested that a behavioural phenotype that is qualitatively similar to but more broadly defined in relatives of autistic individuals than in the general population. August et al[7] reported familial aggregation of cognitive impairment in the siblings of autistic probands. Wolff et al[8] interviewed the parents of autistic children and the parents of nonautistic mentally retarded comparison subjects and found that the parents of the autistic children were more often judged to lack emotional responsiveness and empathy, show impaired rapport with the examiner and have histories of oversensitivity to experience, special interest patterns, and oddities of social communication. Piven et al[9] detected significantly higher rates of social deficits in the parents of autistic children than in the parents of children with Down syndrome, using a semi structured personality interview. Bolton et al[10] examined features of autism in the family histories of the first-degree relatives of autistic and Down syndrome probands using semistructured family history interview. The results indicated that the relatives of the autistic probands had significantly higher rates of communication and social deficits and stereotyped behaviours than the relatives of the Down syndrome probands. Piven et al[11] reported similar findings among the relatives in families with multiple incidence autism in comparison with relatives of Down syndrome probands by using same family history method. All of these studies suggested that the genetic liability for autism may be expressed in nonautistic relatives in a phenotype that is milder but qualitatively similar to defining features of autism. Present study was designed to evaluate the rate of childhood autism and autism like features among the first degree relatives of autistic probands.

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Materials and methods

Selection of Autism Families

The study was carried out in the Child Mental Health Outpatient Clinic of the Department of Psychiatry, Bangabandhu Sheikh Mujib Medical University in Dhaka. The present sample consists of first degree relatives of the families of a consecutive series of 65 new cases of childhood autism between July 1998 and June 2000. Childhood autism was assigned according to clinical diagnosis of ICD -10.[12] These autism families included 56 male and 9 female autistic probands. The boy and girl ratio was 6.2:1. Their age ranged between 3 to 13 years with a mean of 5.80(± 2.65) years. Urban rural distribution were 48 and 17 cases respectively. Thirty three cases were predominantly of middle income group followed by 21 and 11 cases of high and low income group respectively.

Selection of Comparison Families

The first degree relatives of same number of families of nonautic cases with some medical problems having no clinically identifiable developmental disorder were selected from children outpatient department of the University for control comparison group in this study. They were randomly recruited matching with age group, sex and socioeconomic condition of the autistic probands.

Assessment of autism and autism like features

Available first degree family members (parents and siblings) of autistic and control subjects were interviewed for assessing the autism. For each, thorough clinical assessment was undertaken using semistructured case assessment sheet. The diagnosis was phenomenologically based according to ICD-10 criteria for childhood autism.[12]

Then, the family were interviewed with a structured family history interview to assess the presence of a range of autistic like features that hypothesized to possibly be generally related to autism. This instrument including operational definition within it was prepared on the basis of family history interview applied by Bolton et al[10] with some minor modifications and exclusion of the items not directly related to autism. It included communication skills, scholastic skills, social behaviour and adult and childhood functioning. Features were rated as absent (rating = 0), mild or probably present (rating = 1) or severe or definitely present (rating =2). The items were grouped into three principal features that parallel the defining features of autism: social impairment, communication impairment and restrictive, repetitive and stereotyped behaviour.

The parents in each family interviewed about themselves and about the siblings of the probands. Information about the first degree family members who were not available also collected from either parents which further strengthened by the reliable informants to avoid extensive involvement due to limited resources.

As the relatives within same family for the autism and autism like features were not statistically independent, the family was treated as the unit of analysis. The comparison was made between autistic families and control families. Statistical analyses involved two tailed t- tests and x^2 tests with Yates' correction.

Results

Sixty-five fathers, 65 mothers and 115 siblings from the first degree relatives of the 65 autism probands and 65 mothers, 65 fathers and 182 siblings from the first degree relatives of the 65 control probands were included in this study. Table-I shows that only one parents and 2 siblings were found to be autistic in autism group. In the control group, no incidence of autism was reported. Another autism father met the criteria for autism on the basis of current behaviour, but no informant was available to detect the presence of autism in childhood and thereby not considered as a case of autism.

First degree relatives of the autism and control probands were compared with total scores of autism like features from Family Diagnostic Interview by means of two tailed t-tests. There was a general excess of scores in autism families. Particularly, the autism fathers and siblings showed higher rates of social impairments, communication impairments and repetitive and stereotyped behaviour than did control fathers and siblings. However, the difference of scores between two groups was too low to reach the level of significance (Table-II).

Analysis of the autism like features among the first degree relatives of the autism and control probands revealed that 11 (16.92%) fathers, 2(3.08%) mothers and 26(22.61 %) siblings had one or more autism like features in the autism group. In the control group 1(1.54%) fathers, no mothers and 5(2.86%) siblings had had autistic like features. Overall, the difference was significant at 5% level. Table -III shows the comparison of the frequency of these features between two groups. More than one feature were recorded among the relatives. The significance of difference between two groups was tested by x^2 using Yates' correction when appropriate for each features. This analysis indicated that overall increased

frequency of autism like features in the all types of first degree relatives of autistic probands was paralleled by increased frequency of individual features. Significantly higher rates of social and communication impairments but not repetitive and stereotyped behaviours were detected in the autism fathers whereas due to very small numbers for meaningful comparison, no difference was found in the autism mothers and controls. The significantly higher rates of social impairment, communication impairment, and repetitive and stereotyped behavoiour were detected in the siblings of the autism group. Statistical comparison of the rates of individual item from the family history interview between the first degree relatives of the autism and control probands was not undertaken because of low rates of occurence to reach significance.

Table-1: *Comparison of existence of autism in the first degree relatives of the families of autism and control probands*

Type of relatives	Autism group		Control group		X^2 sig.
	N	%	N	%	
Fathers	1	1.54	0	0.00	NS
Mothers	0	0.00	0	0.00	NS
Siblings	2	1.74	0	0.00	NS

Table-II : *Comparison between first degree relatives of autism and control probands with total scores of autism like features on Family Diagnostic Interview**

Type of relative	Autism group	Control group	t-test
Fathers	0.9 (±11.71)	0.0 (±00.00)	0.47, NS
Mothers	0.1 (±16.72)	0.0 (±00.00)	0.04, NS
Siblings	1.0 (±09.51)	0.0 (±18.86)	0.66, NS

* Data are expressed as X = SD

Table-III : *Comparison of frequency of autistic features in the first degree relatives of the autism and control probands*

Austistic features	Autism group		Control group		X^2 sig.
	N	%	N	%	
Fathers					
Social impairment	8	12.30	0	0.00	<0.05
Communication impairment	6	9.23	1	1.54	<0.02
Repetitive & stereotyped behaviour	1	1.54	0	0.00	NS
Mothers					
Social impairment	1	1.54	0	0.00	NS
Communication impairment	1	1.54	0	0.00	NS
Repetitive & stereotyped behaviour	1	1.54	0	0.00	NS
Siblings					
Social impairment	18	15.65	1	0.55	<0.01
Communication impairment	13	11.30	3	1.65	<0.01
Repetitive & stereotyped behaviour	7	6.09	1	0.55	<0.05

Discussion

In this study, incidence of childhood autism in the first degree family members of autism probands was found only 4.6% in total which was 0% in the similar family members of the control probands. The difference was insignificant and statistically not analyzable but indicating the risk of occurence of autism among family members. It was estimated that risk of recurrence of autism in families is 6-8.3%.[3] However, the findings of the large scale genetic studies on autism can only evaluate the findings of the present study.

Though quantitative analyses revealed high rate of autism like features among the first degree family members of autistic probands as of control probands, the result was not significant because of low rate of scores. This is partly due to mild form of features existing among the relatives, lack of information from multiple sources, inability to conduct extensive and direct interview and assessment of all the relatives.

In this study, it was revealed that the first degree relatives of autistic probands had familial aggregation of behaviours that was milder than but qualitatively similar to the defining features of autism. This finding broadly simulates and replicates the findings of other studies.[4,5,7,9-11] Within this study, the findings for the fathers and siblings are particularly significant which suggests that genetic liability for autism are possibly expressed through father shared by the siblings. Several twin studies[4-6] support this view partially at least for the siblings, again it needs intensive family genetic study on mode of genetic transmission of the autism phenotype.

To our knowledge, the present study is the first to examine genetic liability for autism among the relatives of the autism probands in Bangladesh. An additional strength of this study is the control comparison sample of children who were nonautistic, having no developmental disorder and more nearer to the general children population. However, there are several limitations in this study. Due to little or no scope of investigations, it was not possible to exclude the aetiologically related co-occurring conditions including fragile X screenings and formal IQ testing was not undertaken due to lack of resources. Further, all the family members were not directly interviewed though information were obtained from reliable informants due to limited resources. All of these factors could create the biasness of the results.

The result of this study suggests the existence of genetically related features of autism which demand to be included in the genetic analyses of autism and indicate the need for further detailed genetic linkage studies.

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