Genetics in Stuttering

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Abstract

This study investigated the role of genetics in the manifestation of stuttering. Thirty families were investigated. Twenty-eight families reported history of stuttering in first and second-degree relatives. Two twin samples were taken, one comprising of monozygotic twins and the other dizygotic twins. Pedigrees were constructed and analyzed to determine the pattern of genetic transmission. Speech samples of the probands were recorded and percent dysfluency was analysed. The results indicated that the risk of stuttering was greater in close/first-degree relatives (54.5%) compared to second-degree relatives (45.4%). Also, stuttering among relatives occured in a pattern indicating vertical transmission of a susceptibility to stutter with sex-modified expression. There was greater concordance for the disorder among monozygotic than among dizygotic twins. In families with positive family history for stuttering, males (88) was genetically more susceptible to stuttering than females (9) (9.7:1). There was no correlation between consanguinity and genetic transmission of stuttering. The proportion of persistent stutteres (19%) among relatives of male probands was higher than the proportion of recovered stutterers (2.3%). Stuttering if familial tends to be of relatively early and gradual onset. Stuttering severity and familial stuttering don't seem to have any relationship. The results are discussed to fit into the single-locus model and multifactorial model.

Introduction

Stuttering occurs when the forward flow of speech is interrupted by a motorically disrupted sound, syllable or word or by a speaker's reaction thereto (Van Riper, 1982). Stuttering is familial and there is evidence for vertical transmission in families (Kidd, Heimbuch & Records, 1981). However, the mechanisms of that transmission are not clearly understood. A variety of hypotheses have been proposed including several genetic models. Although there is evidence that genetic factors are important for the expression of stuttering, no specific type of genetic transmission has been elucidated.

A genetic factor for a disorder is demonstrated by either a specific structural or functional biochemical defect. No such evidence has been obtained for stuttering. In the absence of such data there are at least four other types of studies, which can provide support for the genetic involvement in a disorder of unknown etiology - twin studies, family studies, separation studies, and genetic linkage studies.

In the ***twin method,*** the proportion of twin pairs in which both members are affected (i.e. the pair is concordant) in a sample of monozygotic (MZ) twins is compared with the proportion of concordant twin pairs in a sample of dizygotic (DZ) twin pairs. This method is used primarily to obtain preliminary evidence that genetic factors are important in the disorder being studied. If it is assumed that same sex MZ and DZ twin pairs share equivalent environments then any difference in concordance rates between MZ and DZ twin pairs are due to the fact that MZ twins are genetically identical whereas DZ twins are not. Early twin studies and stuttering examined whether the prevalence of the disorder was increased among

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twins when compared to singletons. The hypothesis was that twinning in and of itself might be a risk factor for stuttering. The rate of stuttering reported for twins varied considerably with Nelson, Hunter & Walter (1945) reporting a rate of 20% and Graff (1955), reporting a rate of 1.9%. Godai, Tatarelli & Bonnani (1976) conducted a study in an Italian population and reported concordance rates of 83% for MZ twins (N=12 pairs) and 9% for same sex DZ twins (n=11 pairs). In a study reported by Howie (1981) care was taken to control some of the potential sources for bias. They studied thirty same sex twin pairs (21 males and 9 females). Seventeen of the twins were MZ and 13 DZ. Of the MZ twin pairs, 12 were males and 5 females. Among the DZ pairs, 9 were males and 4 females. Concordance rates for stuttering were significantly higher for MZ twins (58%) than compared to DZ twins (13%). Together these studies yield evidence that genetic factors are important in the etiology of stuttering. If the two studies are combined, concordance rates are 69% for MZ and 12% for DZ twins. Thus because MZ concordance is significantly higher than DZ concordance, these twin studies are consistent with the hypothesis that genetic factors are important in the expression of stuttering. However, these results provide little information regarding the specific genetic mechanisms involved.

Studies on ***biological families*** can also yield data suggesting genetic involvement for any given illness and can be used to test specific transmission hypothesis. The family study method consists of comparing rates of illness in families ascertained through an affected individual (the proband) with rates in the general population or with rates in families ascertained through unaffected persons (controls). If the risk of a disorder in families ascertained through an affected person is significantly greater than the risk of the disorder in the population or in the control families, the disorder is familial. This suggests the possible role of genetic factors for the illness. However as with twin studies, if a major environmental component is involved in the etiology of the trait in question, results drawn from family studies will be unable to prove the existence of genetic factors. Data from families can, however be used to demonstrate that vertical transmission occurs. Once vertical transmission has been established, the patterns of illness within families can be compared to those expected under a variety of specific genetic hypotheses. It is assumed that if the pattern of illness within families follows closely a pattern predicted by classical Mendelian hypothesis, it is unlikely that environmental factors could be solely responsible for the transmission.

Andrews & Harris (1964) reported an increased rate of stuttering, among relatives of stutterers. In addition they found that relatives of female stutterers were at greater risk than were relatives of male stutterers. Kay (1964) included information about sex of the proband and sex of the relative in the calculation of risks for first-degree relatives. He found that male relatives of a stutterer (fathers, brothers and sons) are at a greater risk than are female relatives of a stutterer (mothers, sisters and daughters). Kidd, Kidd & Records (1978) and Kidd Heimbuch & Records (1981) found similar risks among first-degree relatives of stutterers. In these studies, the overall risk for stuttering among the first-degree relatives was about 15%. However, distinct differences were obtained between the sexes. The overall rate of stuttering among the relatives of females was 18%, compared to among 14% among relatives of males. When the relatives were separated by sex, additional differences were observed. Stuttering occurred in about 20% of male relatives and 5% of female relatives of male stutterers. Among relatives of female stutterers, approximately, 25% of male relatives and 12% female relatives stuttered. Thus the available family data provide evidence that, stuttering is familial and that specific patterns of vertical transmission occur which appear to be related to the sex of the proband and the relative.

Using this information, specific genetic hypotheses have been examined. Meyer (1945) and Andrews & Harris (1964) found several simple models of transmission, including

autosomal dominant, autosomal recessive and X-linked inheritance, to be compatible with the familial patterns observed. Kay (1964) proposed that either a single gene with polygenic background or polygenic model might account for the data. Kidd (1977) showed that patterns of transmission of stuttering in families were compatible with both a multi-factorial polygenic model and a single major locus model with sex specific thresholds. Kidd's analyses incorporated only summary risk estimates for specific type of relatives. With these kinds of analyses, information regarding the specific patterns of transmission within each family is lost. Cox, Kramer and Kidd (1984) suggested that discrimination among alternative genetic models might be possible with fuller utilization of family data by segregation analysis.

Segregation analysis allows examination of the pattern of transmission in intact families and therefore has more power than previous methods, which relied on summary frequency data. Cox et al. (1984) performed segregation analysis on a subset of families studied by Kidd and co-workers (Kidd, 1977; Kidd et al., 1978; Kidd et al., 1981) and found that transmission of stuttering observed in those families could not be adequately explained by segregation of a Mendelian major locus. However, the familial patterns could be explained by polygenic transmission.

Although the Yale family study of stuttering is by far the largest to date, there are still a number of difficulties with the study. First of all the data about first-degree relatives was obtained through one informant. The vast majority of the first-degree relatives were not seen and evaluated personally. A second shortcoming of these studies is that it is assumed in all of the genetic analyses that the trait being studied is etiologically and genetically homogenous. Given what is known about stuttering, this assumption is most likely to be wrong. If stuttering were heterogeneous, then the assumption of homogeneity would invalidate all of the segregation analyses performed.

There are at least two other methods available, which provide evidence for genetic factors- Separation studies and linkage studies. Neither type of study has been applied specifically to stuttering. ***Genetic linkage*** is detectable at least in theory, if a known genetic marker locus is sufficiently close to a locus affecting the trait under study so that non-random segregation of alleles at the two loci results in an association of phenotype in the family. The demonstration of genetic linkage requires family studies showing that alleles at two separate loci are physically close on the same chromosome. Family data are used to estimate how frequently, the alleles at the two loci are transmitted to a child in combinations different from those in the parents. The degree of linkage is measured as the recombination fraction (the frequency of such new combination) and can range from zero (complete linkage) to 0.5 (independent assortment). The minimum recombination frequency of zero is found for alleles that were always transmitted in the same combinations from generation to generation. The maximum recombination fraction of 0.5 is found for alleles (at two separate loci) that have the same likelihood of being transmitted in new combinations as in the same combination from generation to generation. The maximum recombination fraction occurs for alleles at loci far apart on the same chromosome and of course, for alleles at loci on different chromosomes. Hence, maximum recombination is just another way of phrasing Mendel's second law of independent assortment. Linkage results in the violation of the law.

Some methodological problems in detecting linkage in human data include small family sizes, the inability to control mating and the small probability that the two loci are linked. Historically, the method has had limited applicability, chiefly because of the small number of sufficiently polymorphic genetic markers that were available for humans. This has changed rapidly because of the advance in genetics brought about by recombinant DNA techniques. This class of polymorphisms is referred to as "restriction fragment length polymorphisms" (RFLPS) because they were visualized as inherited variations in length and

defined fragments of DNA when it is digested with specific restriction enzymes. It should be anticipated that this methodology would also be useful in attempts to learn more about the underlying genetic factors, which may be important for the expression of stuttering.

As is evident from this brief review, little is known about the genetics of stuttering. New family studies are needed which use state of art methods. In addition to carefully assessing the proband, all members of the family need to be evaluated personally. It is critical in a family study to know every person who has stuttered at some period in his or her life. Only with data like these it will be possible to test with confidence specific genetic hypotheses. In this context, the present study was planned. The aims of the study were multifold and were as follows:

1) To determine
   a) pattern of genetic transmission in families
   b) pattern of genetic transmission in twins and
   c) To determine male- female ratio in stuttering
2) To investigate the relation between
   a) consanguinity and genetic transmission
   b) age, nature of onset of stuttering and familiality
   c) the persistence and recovery of stuttering and familial stuttering and
   d) familial stuttering and stuttering severity.

Method

Among the four types of data which can give information on the importance of genetic variation in determining who is and who is not susceptible to stuttering (family studies, twin studies, adoption studies and genotyping), family study design and twin study were used in the study.

Subjects

Family study: Twenty-eight families with positive family history for stuttering were selected for the study. Families with stuttering from one to four generations were chosen. The diagnosis for stuttering in the family members was made by a trained speech-language pathologist. Any stutterer with known mental retardation, epilepsy, cerebral palsy or neurological disorders that might be suggestive of generalized neurological dysfunction was not considered for the study. Since gene frequency is a parameter in genetic models and different ethnic groups often have different gene frequencies, only individuals belonging to the Dravidian family were considered for the study.

Twin study: Two twin studies were undertaken. One set of twins was dizygotic different sex pair and the other was monozygotic same sex pair.

Procedure: In the family study design, the affected individual identified by the investigator is called the *"proband"*. After the proband was selected, information about the family members was obtained using the proband (or parents) as the primary informant ("family history method") or assessing the status of relatives directly (the "family study method") using a questionnaire. Detailed information was obtained about the age and nature of onset of stuttering, consanguinity, persistence and recovery of stuttering in families. Pedigree analysis was done. The pedigree included all the first and second-degree relatives of the proband. Standardized symbols were used in the construction of a pedigree. Conversation samples of all subjects with stuttering were elicited and audio recorded.

Analyses: The pedigrees were used to analyze the following areas in genetics of stuttering.

1) Pattern of genetic transmission in families
2) pattern of genetic transmission in twins
3) male-female ratio in stuttering
4) consanguinity and genetic transmission of stuttering
5) persistence and recovery of stuttering as related to heredity
6) relation between age and nature of onset of stuttering and familiality in stuttering
7) relation between familial stuttering and stuttering severity.

The speech samples were verbatim transcribed to find out percent dysfluencies. Percent dysfluencies was calculated using the formula: Percent dysfluency = Number of dysfluencies x 100 / Total number of words. Percent dysfluencies were used as a measure of severity of stuttering which was correlated with familial stuttering. Attempt was also made to fit the results of the study to any one genetic model of stuttering.

Results and Discussion

I) Familiality and pattern of genetic transmission of stuttering in families

The first-degree relatives had a higher percent of stuttering (54.5%) compared to second-degree relatives (45.4%). This suggests a greater risk for stuttering among the first-degree relatives than among second-degree relatives. Among the first-degree relatives, brothers, grandfathers and cousin brothers had a higher percent of stuttering compared to others. Among the second degree-relatives, paternal uncles, maternal uncles and grand uncles had a high percent of stuttering. This shows that there are more males than females affected among both first and second-degree relatives.

Table 1 shows the frequency of stuttering among first-degree relatives and table 2 shows the frequency of stuttering among second-degree relatives.

Table 1: Frequency of stuttering among the first- degree relatives.

Relation	No.	% of stuttering	Relation	No.	% of stuttering	Relation	No.	% of stuttering
Father	10	15.2	Grandfather	6	9.09	Cousin brother	9	13.64
Mother	2	3	Grandmother	0	0	Cousin sister	1	1.5
Brother	6	9.1	Great-grandfather	0	0			
Sister	2	3	Great-grandmother	0	0			
Total	20	30.3		6	9.09		10	15.15

When the pedigrees are observed some pedigrees indicate direct transmission (from father or mother) while others indicate indirect transmission (from other family members). Results showed a 50% vertical transmission when the proband was a male. This is in agreement with the results obtained by Kidd et al., (1981). In the present study even for a female, there was 50% vertical transmission. Also, the transmission of the characteristics of stuttering increases when the father of the proband is also a stutterer (Kidd et al., 1981).

Table 2: Frequency of stuttering among the second- degree relatives.

Relation	No.	% of stuttering	Relation	No.	% of stuttering
Maternal uncle	5	7.58	Grand uncle	6	9.1
Maternal aunt	0	0	Grand aunt	1	1.5
Paternal uncle	10	15.15	Others	7	10.6
Paternal aunt	1	1.5			
Total	16	24.2		14	21.2

II) Pattern of genetic transmission in twins

Results from the two twin samples taken for the study indicated that pair was concordant while the dizygotic pair was discordant monozygotic for stuttering. This supports the earlier findings on higher concordance rates for MZ twins when compared to DZ twins as reported by Howie (1981) and Godai et al., (1976). This gives a strong support for stuttering being a genetic disorder.

III) Male to female ratio in stuttering

Combining family studies and twin studies, total number of males with persistent stuttering was 88 when compared to 9 females. These included all relatives of male and female probands and the probands themselves. This gives a male: female ratio of 9.7:1. This shows that males are more susceptible to stuttering than females. This is in concordance with the results obtained by Kidd et al., 1978; Kidd et al., 1981 who report sex effect as high as 6:1 (male vs. female). The ratio obtained in this study is higher compared to those obtained in earlier studies. It may be because (a) females are not brought for fluency evaluation as importance is not given to their speech, or (b) the ratio itself was high in the present study.

IV) Relationship between consanguinity and stuttering

The study did not reveal any significant relation between consanguinity and genetic transmission as there was not much difference seen in the number of stutterers between consanguineous and non-consanguineous families.

V) Persistence and recovery of stuttering as related to heredity

The results indicated that persistent stutterers among relatives of male probands (19%) was higher than the proportion of recovered (2.3%) stutterers. Also, there were greater proportion of recovered stutterers among the first-degree relatives (1.5% and 8.3% in males and females, respectively) than among the second-degree relatives (0.7% and 3.2%, males and females respectively).

VI) Relation between age and nature of onset of stuttering and familiality

Most probands taken for the study reported childhood and gradual onset of stuttering. This gives more support for stuttering to be genetically transmitted in families of these probands. One subject reported stuttering onset after a road accident following which he had lost his consciousness for a day. This subject reported stuttering in the immediate family members, which goes to show that the subject might have been genetically susceptible to stuttering and this could have led to the manifestation of the disorder following the accident (environmental condition). A special reference to this model is the sex specific threshold model described by Kidd et al., (1978) who proposed that stuttering genotypes are expressed as different susceptibilities based on sex. Stuttering threshold is hypothesized to be lower for males. Hence, lesser

precipitating (genetic or environmental) factors that contribute to stuttering are sufficient for the disorder to be manifested in males.

VII) Relation between familial stuttering and stuttering severity

The results indicated that stuttering severity was significantly much more (30.84%) in probands whose fathers or mothers did not have had stuttering than in probands (20.8%) whose parents had stuttering. This is in agreement with the results of Andrews & Harris (1964) who found that the presence or absence of a positive family history of stuttering did not seem to be significantly related to the severity of stuttering.

The questions to be answered are many. The initial question is whether there is a transmission of stuttering from parent to offspring. The data from the present study shows stuttering is very frequent in these families but do not exclude the possibility that the presence of stuttering has a random pattern in these families. Of the 30 families 11 stutterers had either parent stuttering while 19 stutterers had neither parent stuttering. Is there really a consistent pattern of transmission within these families? To test the null hypothesis that the pattern is random, the data was divided in to 4 groups as in table 3.

Table 3: Stuttering in proband's parents (N-neither parent ever stuttered; F-father ever stuttered; M-mother ever stuttered; B-both parents ever stuttered; % BS-% brothers stuttered; % SS - % sisters stuttered).

Proband	N	F	M	B	% BS	%SS
Male	60.7			0	22.2	8.7
		35.7	3.6		25	0
Female	50			0	0	0
		0	50		0	0

The frequencies of stuttering among brothers and sisters show a remarkable difference. If neither parent of the male proband ever stuttered, 22.2% of the brothers stuttered and 8.7% of the sisters stuttered. But, if the father had stuttered, the frequency was 25.0 % and 0%, respectively. In case of female probands the frequency was 0%.

In approaching the genetics of stuttering several different genetic hypotheses have been considered. Two specific ones will be discussed; both of them explain the data and yet are extremely different.

The first model is the multifactorial-polygenic model. According to this model, the genetic susceptibility is inherited as a function of many genes and each one of these genes contribute only a very small amount. The population distribution for this underlying susceptibility is basically a bell-shaped curve. In addition to an individual's susceptibility, there are physiological or developmental thresholds such as individuals who have susceptibility above that threshold are affected. In addition to the genetic components determining this distribution, there are nongenetic components. One of the measures of the degree of genetic vs. nongenetic components is the degree of displacement of the distribution for relatives from the mean of the population. Relatives of an unaffected proband are displaced upwards, on an average if there is a genetic component to susceptibility. The physiological threshold remains the same so that there is a higher proportion of relatives affected than one would expect for unrelated individuals in the general population. It has already been seen that in stuttering the percentage of relatives who stutter is much higher than in the general population. The multifactorial-polygenic model can be made more appropriate for stuttering by specifying different thresholds for two sexes. Kidd (1977) analyzed the sex-

specific model and gave the following predictions: (a) the parent-offspring correlation and the sibling correlation are 38%, (b) the predicted male lifetime prevalence is about 4%, and (c) the female lifetime prevalence is 2%. In the present study the parent-offspring correlation is 27.2% and the sibling correlation is 16.6 %. These factors in the multifactorial-polygenic model give a very good fit to the available data.

The other model is the single major locus model. One gene locus with two alleles gives rise to 3 genetic types: homozygotes or the normal allele, heterozygotes and homozygotes for stuttering allele. The non-genetic factors are hypothesized to affect the distribution of susceptibility around the mean of each genotype. Thus, the model has the same sort of susceptibility scale as the multifactorial-polygenic but each genetic type has a different average liability. The frequencies of the genetic types are determined by the allele frequencies. A threshold is postulated and individuals above the threshold are affected irrespective of their genetic constitution. Hence, in this model, even normal individuals, if they have a sufficiently exacerbating environment can be affected, whereas carriers of the gene, if they have sufficiently ameliorating environment can be unaffected. When this model is applied to the data the results were as in table 4.

Table 4: Fit of the single-major-locus model to the family incidence data on stuttering.

	Total population	No. of stutterers	No. of nonstutteres	Percent of stuttering
Males	329	88	251	26.7
Females	296	9	287	3.0
Total	625	97	538	15.52

The results predict that the frequency of stuttering is about 15.52%. The proportion of individuals with a specific genetic type who actually manifest stuttering is called the penetrance for that genotype. The model predicts very low penetrance values for the homozygous normals and very high penetrance values for homozygotes for the hypothetical stuttering gene – homozygotes are always affected whether male or female. The gender effect and all of the environmental effects are manifest in the penetrances of the heterozygote, the individuals who have both types of genetic information. However, no good data are available for these predictions. The differences in gene type frequencies between male and female stutterers can help explain the transmissional aspects of stuttering. A female stutterer is much more likely to carry the stuttering gene. A female to be a stutterer must have received the gene from both parents proportionately more often than a male and hence will proportionately more often transmit the gene to all children. Though the model initially considers all stuttering as the same, it nonetheless predicts a sort of heterogeneity among stutteres.

Though the understanding of the genetic aspects of stuttering is not definitive, these analyses have implications for research into the causes of stuttering. Future work can consider separately transient childhood stuttering and stuttering that persists into adulthood. Further, the statistics behind the genetic models are very simple and ignore some potentially useful information in the data. Better statistics and biologically more realistic models are required.

Also very important will be the data more closely reflecting the particular inherited susceptibility. Information on laterality and on some response to dichotic listening tasks within families will be potentially useful. It may be that in some families there exists a clear genetic pattern of abnormal cerebral processing that does not always result in stuttering but at least in those families, it is always necessary for stuttering to develop.

The results emphasize that gender is a vital factor. Research and treatment of stuttering must consider the gender of the patient. The results also demonstrate that transmission of stuttering exists which can be explained with genetic hypothesis. Finally, the results point out that research on stuttering, as in many other types of research on human disorders, a genetic perspective is essential.

Conclusions

The findings of the study are consistent with the hypothesis of genetic transmission, but none can rule out a significant role of non-genetic factors. The multifactorial-polygenic model and the single locus model can be applied to the findings of the study. Fitting the data into the single-locus model predicts the incidence of stuttering to be 15.52%. Thus, genetic susceptibility possibly necessary but certainly not sufficient, is a major factor in stuttering. Moreover, females are more resistant to an inherited susceptibility to stuttering than males.

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