INHERITANCE OF CONGENITAL ESOTROPIA*

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INTRODUCTION

ALTHOUGH THE LITERATURE CONTAINS NUMEROUS REFERENCES TO FAMILIAL AG-
gregation of strabismus,[1-3] multiple questions remain as to the precise
mode of transmission. Are we dealing with a polygenic trait, as is com-
monly believed or a Mendelian trait, or even a nongenetic disease? The
older analyses often dealt wih strabismus as the phenotype rather than
with specific subtypes, such as accommodative esotropia, exotropia, or
congenital esotropia. If such pooling were valid, analysis should give the
same results in the subtypes as in the aggregate sample. In addition,
conclusions were drawn from individual pedigrees, but to date none of
the analyses have employed modern segregation analysis of large groups
of families sampled in a systematic way with consistent clinical defi-
nitions. Thus, in spite of multiple extensive investigations into a possible
genetic basis for eye disorders such as this, the question of etiology is
unsolved to date, and hence this study was undertaken.

MATERIALS AND METHODS

A total of 173 pedigrees comprising 1589 people were collected. The
sample consisted of three subsets of data: (1) 37 patients operated on by
Costenbader, and who are now at least 25 years old, were ascertained and
their children examined. Thus, this subset was ascertained through an
affected parent; (2) a group of 83 families were seen by one of us (JTF) at

the University of Miami; (3) a group of 53 families were similarly ascertained through a patient with congenital esotropia diagnosed at the Wilmer Institute of the Johns Hopkins Hospital. The pedigrees included information on the proband, the siblings, the parents, the parents' siblings, and grandparents, thus, included as a minimum all second degree relatives. All probands had a diagnosis of esotropia made prior to age 6 months in the absence of refractive errors of more than $+1.50$ diopters spherical equivalent.

   First degree relatives as well as more remote relatives had an evaluation of their muscle balance where possible. In many instances old records were evaluated, in other cases an ocular history only was obtained. Cases with mental retardation, cerebral plasy, neurodegenerative disease were excluded. However, small angle deviations in relatives unaffected by history and not examined, would have been underdiagnosed.

   Segregation analysis was done on the three samples and on the aggregate of all 173 pedigrees using the Pedigree Analysis Package (PAP).[4,5] In this analysis, maximum likelihood estimators (MLE) of gene frequency, penetrance, and transmission of alleles between parents and offspring were estimated as a series of models were examined. First, a nongenetic, sporadic model of inheritance was fit, where all individuals were assumed to have the same genotype and the conditional probability of expressing the esotropia phenotype (ie, penetrance) was estimated. Secondly, a single locus Mendelian model was fit where the allele frequency under Hardy-Weinberg equilibrium was estimated along with the penetrance for the various genotypes. Lastly, a generalized single locus model was examined where the probability of transmitting this putative allele was estimated along with its frequency and penetrance. The Mendelian model of inheritance represents a subset of this generalized model where these transmission probabilities are set to predefined values.

RESULTS

Initially the individual pedigrees were analyzed by hand and overall were felt to be compatible with an autosomal inheritance pattern with disease occurring in the homozygous affected. The majority of pedigrees showed isolated affected cases (113 of 173), in 60 pedigrees there were 2 or more affected (Table I). Pedigrees with two or more affected offspring of normal parents, suggest disease in the homozygous, or classic autosomal recessive inheritance (Fig 1A). There were other pedigrees in which a nonaffected married an affected and produced both affected and nonaffected children, suggesting the nonaffected parent was a heterozygote for the

TABLE I: NUMBER OF AFFECTED INDIVIDUALS PER PEDIGREE

DATA SET	PEDIGREES WITH 1 AFFECTED	PEDIGREES WITH 2 AFFECTED	PEDIGREES WITH 3 AFFECTED	PEDIGREES WITH 4 AFFECTED	PEDIGREES WITH 5 AFFECTED	TOTAL NO. OF PEDIGREES
1	24	10	3	0	0	37
2	53	23	3	3	1	83
3	36	14	3	0	0	53
Total	113	47	9	3	1	173
Total no of affected	$\times 1$ 113	$\times 2$ 94	$\times 3$ 27	$\times 4$ 12	$\times 5$ 5	251 Total affected individuals

TABLE II: SEGREGATION ANALYSIS OF CONGENITAL ESOTROPIA OF 1589 INDIVIDUALS IN 173 FAMILIES ASCERTAINED THROUGH AN AFFECTED PROBAND

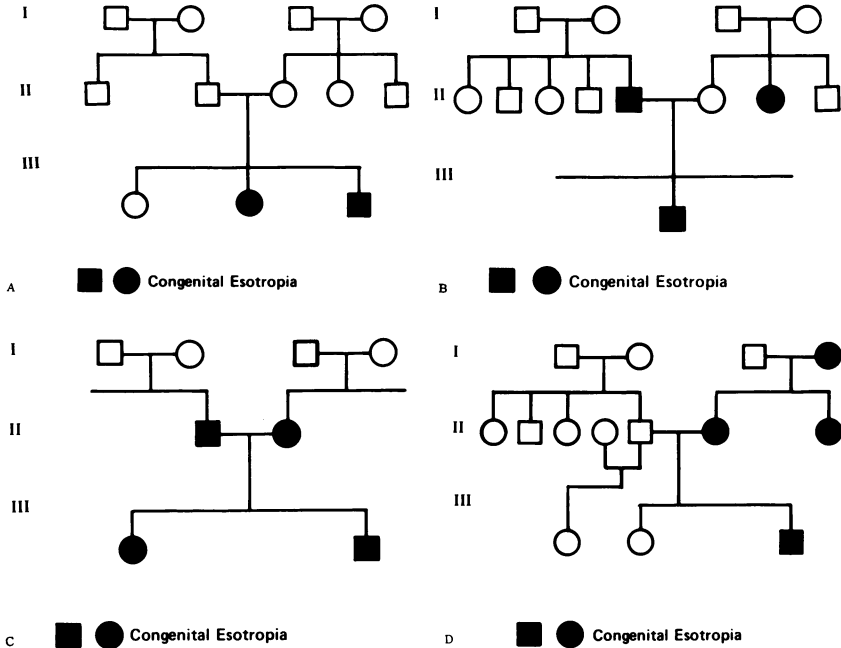| MODEL	LOG L	NO. OF PARAMETERS	GENE FREQUENCY	PENETRANCE		
				P (Aff/AA)	P (Aff/Aa)	P (Aff/aa)
Sporadic	-312.54	1	1.0	0.0581 ± 0.0625	—	—
Mendelian dominant	-304.59	3	0.050 ± 0.045	0.1829 ± 0.0746	0.1829 ± 0.0746	0.0146 ± 0.0117
Mendelian codominant	-297.82	4	0.092 ± 0.103	0.767 ± 0.641	0.0516 ± 0.0696	0.0050 ± 0.0146

FIGURE 1

trait (Fig 1B). There was one pedigree in which two affected had all affected offspring, which is also compatible with the above hypothesis (Fig 1C). The prevalence of esotropia in the general population is usually estimated as about 1%.[1,6-8] Given this estimated prevalence of 1% in the population one would expect, under a single locus model with complete penetrance in the homozygous affected, that about 1 in 10,000 matings have such an affected by affected mating. One pedigree was best compatible with disease in the heterozygote or autosomal dominant inheritance (Fig 1D). However if one takes into consideration the relatively high gene frequency predicted under the simple homozygous Mendelian model (18% of the population), one realizes that an affected individual has about a 1 in 5 chance of marrying a heterozygote. The probability of this occurring twice in consecutive generations is 1 in 2500 which could explain the pedigree in Fig 1D.

Using the PAP,[5] MLE for penetrance (the probability of being affected conditional on genotype), allele frequency, and transmission were obtained for 173 pedigrees ascertained through a proband with congenital esotropia (Table II). An approximate ascertainment correction was made in this analysis by conditioning on the likelihood of the proband (ie, the

likelihood of the proband alone was substracted from the unconditional likelihood of the model on the entire pedigree). As seen in Table II, a sporadic model, which assumes that all individuals have the same genotype, estimates the probability of having esotropia (ie, the penetrance) as 0.058 ± 0.063. Although not shown here, a similar model was examined where separate penetrances were estimated for males and females, but this was not significantly different from this sporadic model with equal penetrance in males and females, so the expression of putative genotypes was held constant for both sexes in all subsequent analyses. The three subsets of data showed equal probabilities and had been pooled.

Also shown in Table II are two single locus Mendelian models of inheritance. In the first, the penetrance of the AA and Aa genotypes were held constant (in effect requiring the "A" allele to be dominant to the "a" allele), while in the second three separate penetrances were estimated simultaneously (this corresponds to a codominant model). When a dominant model was considered the penetrance of the two abnormal genotypes was estimated as $18\% \pm 7\%$, while the third genotype was estimated to have a very low penetrance ($1.5\% \pm 1.1\%$). This Mendelian model gave a substantial improvement in the log-likelihood of the model and a chi-square statistic testing the hypothesis that $P = 1$ and all penetrances are equal leads to rejection of the sporadic model for these data ($\chi^2 = -2 \times [-312.54 + 304.59] = 15.89$ with 2 dF, $P < 0.01$). Under a more general Mendelian model were all three genotypes are allowed to have different probabilities of being affected, the expression of the esotropia phenotype appears to be largely confined to a single genotype with some small risk to the other genotypes (Table II). The gene frequency under this model remains low ($P = 0.09$), leading to very large standard errors about the estimated penetrance values seen in Table II. This codominant model represents a statistically significant improvement in the log-likelihood of the model and would lead us to reject the null hypothesis of equal penetrances required under straight dominant or recessive models.

As a further test of Mendelian inheritance, the probability of transmitting the putative "A" allele for esotropia from a heterozygous parent was estimated using the MLE shown in the last row of Table I. The estimated value of this transmission parameter (0.79 ± 0.04) appeared substantially different from the Mendelian expectation of 0.5 for these data, raising the distinct possibility of etiological heterogeneity among these families.

PAP cannot be used for multifactorial inheritance of pedigree data in the absence of metric data. The results expected from such an analysis, however mask the existence of heterogeneity and only give an overall liability value of the disease or heritability.

DISCUSSION

To maximize homogeneity in the clinical phenotype, only probands with congenital esotropia diagnosed prior to age 6 months in the absence of a major refractive error were included. Richter[1] showed a 94.1% concordance in monozygotic twins for this clinical definition while 26% of dizygotic twins were concordant for strabismus only, thus, making an abnormal intrauterine environment as well as other familiar factors a very unlikely cause of strabismus, but suggesting a strong genetic component.

The results from this analysis of 173 families are compatible with a Mendelian codominant model, with a high probability of being affected for homozygotes carrying a relatively common allele. The standard errors from this analysis are very large, however. The estimated transmission probability for this codominant model is substantially different from the Mendelian expectation, suggesting the existence of etiologic heterogeneity among the families, which would result from admixture a major proportion of autosomal recessive cases, some dominant cases, and possibly aggregation of nongenetic cases.

Certainly the phenotype, strabismus, is far away from the genotype and we still have to do further detailed studies on disorders of this type. Clinical and psychophysical measurements are presently collected to assess sensory functions in parents and presumed normal sibs of probands with congenital esotropia, to detect evidence of minor manifestations of the gene.

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DISCUSSION

DR RUFUS O. HOWARD. The authors are to be congratulated for their new contribu-
tion to an old problem: the inheritance of strabismus. Approximately 24 centuries
ago, Hippocrates reported a familial tendency to strabismus: ". . . the children of
parents having disturbed eyes squint also for the most past." The next significant
understanding followed definition of the principles of inheritance by Mendel in
1876. Early in this century, many clinical reports of esotropia were published with
different modes consistent with autosomal dominant, and autosomal recessive
inheritance; only rare reports were attributed to x-linked inheritance. Surveys of
different families with esotropia between 1910 and 1950 claimed herditary factors
in 20% to 50% of all patients with esotropia. However, during these same years,
many factors were recognized to influence esotropia, and in 1961, François sum-
marized this confusion when he wrote "the laws governing inheritance of strabis-
mus . . . are rather poorly defined." This confusion persists to the present, for in
the current edition of McKusick's Mendelian Inheritance in Man, no definite
mode of inheritance is accepted for esotropia. Several factors which are recog-
nized to result in strabismus include ametropia, amblyopia, anisometropia, con-
vergence activity, binocularity, ARC, neural factors, muscle paresis, etc. Twin
studies have suggested that refractive factors are inherited. The relative impor-
tance of each factor for esotropia is not known:

In this study, only patients with esotropia onset prior to age 6 months, and
refractive errors less than + 1.5 D were included. On the basis of a prior study by
Richter, this should be a homogeneous clinical group. However, this was not a
clinical study, and other clinical variables were not evaluated. A clinical evalua-
tion of this same group of patients would clarify the genetic uniformity of reported
patients.

The new approach taken by the authors involves a statistical analysis of data.
This selected group of patients, with esotropia evident prior to 6 months, and
refractive errors less than + 1.5 D, were examined for best fit to different models
of Mendelian inheritance. To facilitate this study, a computerized program was
employed. A best fit was obtained with a model of codominant inheritance. This
means that two separate factors could explain the clinical observations. It does not
represent absolute proof that two factors or two genes regulate hereditary esotro-
pia. We must also recognize that all patients in this study may not have the same
genetic defect(s). This study represents an interpretation consistent with codomi-
nant inheritance. We are indebted to the authors for bringing to our attention
these elegant new computerized programs which may be employed to support
our refute hereditary factor(s) in esotropia and other ophthalmologic conditions.

I would like to ask the authors if there is any informative twin data from this
study? How does their data fit a polygenic model? Do they have any clue to the
two clinical factors (or genes) responsible for this special group of patients with
congenital esotropia?

DR SUZANNE VÉRONNEAU-TROUTMAN. I would like to ask Doctor Maumenee two
questions. The first one concerns the classification of esotropia. We know that

truly congenital esotropia, that is, present at birth, is rare. On the other hand, esotropia, not truly congenital, but with onset before 6 months is more frequent. It is better termed "early onset" or "infantile esotropia." As both groups differ in their clinical pictures as well as their prognosis, have the authors made this distinction in their attempt to study the inheritance of so-called "congenital esotropia?"

My second question concerns the coexistence of esotropia and exotropia in the same family.

Some years ago, Doctor Abraham Schlossman stated that he had never obser-vered the coexistence of exotropia and esotropia in the same family. I have made several such observations, without being able to establish the presence of two different pedigrees in the ascendents. Is a weakness of the binocular state trans-mitted with all possible manifestations, or a definite type of strabismus? Have the authors made such observations in their study of esotropia with onset before 6 months?

DR MARSHALL M. PARKS. I enjoyed this paper although much of the advanced genetics was beyond my understanding. What I know about the entity of congeni-tal esotropia was learned after it became apparent that sorting out the congenital from the acquired entity was the first step to comprehending this complex disor-der. From the patients identified as having the entity of congenital esotropia we learned a great deal about binocular vision. Unless the esotropic eyes were aligned within a critical period that lasted only during the first 2 years of life, binocular vision never developed. Secondly, we learned about the difference between macular and extramacular binocular vision since practically none of the congenitally esotropic patients aligned during the critical period developed macu-lar binocular vision despite their high success rate for development of extramacu-lar binocular vision.

In addition to the sensory knowledge we have picked up about congenital esotropia we also have learned something about the motor aspects. Practically all patients with congenital esotropia manifest dissociated vertical deviation (DVD) if studied closely during their first decade of life. Another important link in our more complete understanding of congenital esotropia is that not all patients with DVD have a history of heterotropia. Many have grossly appearing straight eyes. Yet, regardless of whether their eyes have always been straight or whether their congenitally esotropic eyes were straightened during the critical period for devel-opment of binocular vision, patients with DVD have only extramacular binocular vision.

Concerning the hereditary features of this entity called congenital esotropia, it is apparent that a high percentage of first-order relatives have the esotropia while others have DVD without esotropia and still others have neither esotropia nor DVD, but have only extramacular binocular vision. From these observations I propose the hypothesis that congenital esotropia is only one of the motor compo-nents that may be expressed in a hereditable sensory disorder characterized by absence of macular binocular vision. The penetration of the congenitally esotropic component is variable, but probably less than the DVD component.

DR LEONARD APT. We are well aware that parental consanguinity is a strong indicator of autosomal recessive inheritance. This factor undoubtedly was analyzed by Doctor Maumenee and co-workers.

My question then is: did parental consanguinity play a significant role in their study? This information may prove useful because if indeed it was a factor then we have further evidence for a recessive inheritance pattern. Also, in genetic counseling we know that the chance of a subsequent offspring likewise having congenital esotropia is greater if the parents are related.

DR IRENE H. MAUMENEE. I would like to thank all the discussants, but first of all Doctor Rufus Howard for his erudite discussion giving us the history of the study of congenital esotropia going back to antiquity. The data have not been analyzed for multifactorial inheritance. This program does not perform such an analysis in the absence of metric data, which we did not have a sufficient number of in the parents. Hence, this was deferred. Eighty-three of the pedigree were contributed by Doctor Flynn, his data included metric information in 1st, 2nd, and 3rd degree relatives and should prove useful information if further families are added. We are far from knowing exactly what the gene does, but understanding that a major, possibly recessive gene, is at the basis of this condition may lead us toward looking at some biochemical defect, for example a neurotransmitter disease. Hence, this is a significant finding. However, we are far away from knowing what the molecular defect is or at what level the abnormal gene function occurs. We do not have any, but the most rudimentary study of genetic parameters of this entity. The second point with regard to the question of Doctor Parks, I think we are dealing with admixture of several entities here and it is hard to clearly define subtypes unless one has even larger pedigree numbers. However, we are going ahead and use the most up-to-date computer technology to test hypotheses of inheritance. With regard to Doctor Apt, consanguinity only becomes an important factor in manifestation of a disease if the disease in question is rare. If the disease state is as common as congenital esotropia, then the heterozygous frequency in the population is about 20%, thus random mating has a probability of 10% of resulting in similarly affected children under a recessive hypothesis. Hence, one does not have to marry a cousin in order to bring out this defect. Regarding Doctor Véronneau-Troutman's question, I have seen exotropia as well as esotropia in the families. They are both frequent conditions and the question whether they occur both by chance in one family or whether they are effects of the same gene defect, has not been resolved. We try to initially analyze as pure data files as possible, restricting ourselves to a single phenotype. That question will possibly be resolved as a by-product, if the parameters of inheritance for separate phenotypes should differ.