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ORIGINAL INVESTIGATION

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Inheritance of migraine investigated by complex segregation analysis

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Abstract Migraine is the most common neurological disorder, affecting about 20% of adults. The mode of inheritance was analyzed in the two main types of migraine, migraine without aura (MO) and migraine with aura (MA), by complex segregation analysis using the computer program POINTER. We included 126 probands with MO and 127 probands with MA from the general population. First-degree relatives and spouses were blindly interviewed by a neurological research fellow. The complex segregation analysis indicated that both MO and MA have multifactorial inheritance without generational difference.

Introduction

Migraine is the most common neurological disorder, affecting about 20% of adults (Rasmussen and Olesen 1992; Russell et al. 1995). Affected persons typically suffer from migraine for a major part of their lives at considerable personal and socioeconomic expense (Rasmussen et al. 1992; Cull et al. 1992). There are two main types of migraine (Headache Classification Committee of the International Headache Society 1988). The first, migraine without aura (MO; previously called common migraine), is characterized by headache attacks lasting 4–72 h. The headache is usually severe, unilateral, pulsating, aggravated by physical acitivity, and accompanied by nausea, vomiting, photophobia, and phonophobia. In the second type, migraine with aura (MA; previously called classic migraine), the attack is initiated by aura, i.e., reversible visual, sensory, speech, or motor symptoms. The ensuing headache is very similar to that of MO. However, differences in regional cerebral blood flow (Olesen et al. 1981a, b) and the distinctly different clinical features (Russell et al. submitted) suggest that MO and MA are separate disorders. This is further supported by the specific family pattern of probands with MO and MA (Russell et al. 1993; Russell and Olesen in press). The prevalence of MO among first-degree relatives of probands with MO and that of MA among first-degree relatives of probands with MA (Russell et al. 1993; Russell and Olesen in press) are statistically significantly higher than the expected prevalence in the general population (Rasmussen and Olesen 1992; Russell et al. 1995). The familial aggregation of MO and MA may be the result of genetic and/or environmental factors. The prevalence of MO among spouses of probands with MO was slightly higher than expected in the general population, but less than the prevalence in first-degree relatives, suggesting a combination of genetic and environmental factors. The prevalence of MA among spouses of probands with MA was not increased, indicating that MA is determined largely or exclusively by genetic factors.

The aim of the present study was to explore the mode of inheritance further with a complex segregation analysis (Lalouel and Morton 1981). This allows testing of hypotheses of inheritance of a major dominant, additive, or recessive gene, and multifactorial genetic or environmental inheritance.

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Materials and methods

Data collection

A sample of 3000 males and 1000 females, all 40 years old and residing in 11 municipalities around the Copenhagen County Hospital in Glostrup was drawn from the Danish Central Person Registry. Data from national statistics (Danmarks statistik 1993a, b) showed that the population in the 11 municipalities was representative of the total Danish population regarding age, sex, and marital status. The probands were found among the sample. All persons

with MA were included as probands. An equivalent number of probands with MO was randomly selected the persons with MO. Probands with among cooccurrence of MO and MA were not included in the segregation analyses. Spouses and first degree relatives aged 18 or above were blindly interviewed by a neurological research fellow experienced in headache research (M.B.R.). The operational diagnostic criteria of the International Headache Society (IHS) were used (Headache Classification Committee of the International Headache Society 1988). The segregation analysis treated those not interviewed as being of unknown status with regard to MO and MA. The primary reason for not interviewing spouses and first-degree relatives was decease. A detailed description of the study design, representativeness of the population, and characteristics of the non-participants have been published elsewhere (Russell et al. 1995; Russell and Olesen in press). The project was approved by the Danish ethics committees.

Statistical analyses

The complex segregation analysis is based on the distribution of the disease in nuclear families (parents and their offspring). Each pedigree ascertained on the basis of the probands can contain one or more nuclear families. The 126 probands with MO belonged to 126 pedigrees, which were split into 164 nuclear families with 376 children; the 127 probands with MA belonged to 127 pedigrees, which were split into 168 nuclear families with 408 children. The analysis required that any relative with MA in the MO group was considered normal and vice versa in the MA group, i.e., only first-degree relatives with the same status as the probands were considered affected. Table 1 gives the combination of phenotypes among the parents and the mating types.

We used a segregation analysis based on the so-called mixed model, which incorporates mendelian inheritance of a single major gene locus, multifactorial inheritance, and transmissible or non-transmissible environmental factors. The model assumes that the liability to the disease can be described by an underlying continuous liability scale (y). The liability of each person is assumed to be determined by: the independent contribution of a major locus (g; a locus that causes a displacement of more than one phenotypic standard deviation between the normal and abnormal genotypes on the liability scale); a multifactorial component (c), attributable in theory to a large number of genetic or environmental influences or both, acting additively and transmitted from parents to their children; and a random nontransmitted environmental factor (e). The individual liability to disease in this model is then $y = g + c + e$. The variance (V) of y is similarly divided into three components: $V = G + C + E$, where G, C and E are the variances of g, c, and e, respectively. The relative contribution of multifactorial transmission is defined by H, the heritability (in the narrow sense), which reflects genetic transmission not ascribed to a major gene, and cultural transmission: $H = C/V$. If Z is a parameter that takes intergenerational differences in heritability into account, then HZ denotes the parental heritability.

The major locus, which is assumed to have two alleles, A and A', producing three genotypes AA, AA', $A'A'$, is defined by three parameters: q, the frequency of the major gene A'; t, the displacement, i.e., the distance measured in standard deviations on the liability scale between the two homozygous genotype class means; and d, the degree of dominance, expressed as the position of the heterozygous class mean in relation to the homozygous class mean ($d = 0$ corresponds to a recessive gene, $d = 1$ to a dominant gene, and $d = 0.5$ to an additive gene).

The affected state is defined by a threshold (T) on the liability scale, which is determined from the morbid risk of disease. For MO and MA, the morbid risk varies with sex and age. Hence, each person was assigned to a liability class based on sex and age. The program used allowed for only nine different liability classes. Eight classes were used for both MO and MA (Table 2). Further details of the analysis are given in Appendix A.

Table 1 Distribution of the 164 migraine without aura (MO) nuclear families and 168 migraine with aura (MA) nuclear families by ascertainment and mating type (N normal, A affected, U unknown status)

Type of selection	Mating type					
	N×N	N×A	A×A	N×U	A×U	U×U
Migraine without aura						
Complete		29	4		5	
Incomplete	25	28	3	33	6	31
Migraine with aura						
Complete		29	1		11	
Incomplete	21	18	7	28	23	30

Table 2 Sex- and age-specific prevalence of migraine without aura (MO) and migraine with aura (MA) per 1000 inhabitants in the county of Copenhagen. The numbers in parenthesis refer to the liability class

Age (year)	Migraine without aura		Migraine with aura	
	Males	Females	Males	Females
10–19	60 (1)	113 (5)	40 (1)	48 (5)
20–29	85 (2)	180 (6)	51 (2)	64 (6)
29–39	93 (3)	201 (7)	63 (3)	96 (7)
> 40	102 (4)	221 (8)	69 (4)	106 (8)

Results

The complex segregation analysis of migraine without aura (MO; Table 3) gave the sporadic model (no family resemblance $H = q = 0$) a poor fit compared with the multifactorial model ($H > 0$; $\chi^2 = 42.65$, $df = 3$, $P < 0.001$). There was no evidence of an intergenerational difference ($Z = 1.31$) for multifactorial inheritance ($\chi^2 = 1.24$, $df = 3$, $P > 0.5$). Neither of the three models that incorporated a major locus ($q > 0$) explained the observed segregation pattern better than the multifactorial model. The complex segregation analyses of migraine with aura (MA; Table 4) gave the sporadic model a poor fit compared with the multifactorial model ($H > 0$, $\chi^2 = 76.17$, $df = 3$, $P < 0.001$). There was no evidence of an intergenerational difference ($Z = 0.75$) for multifactorial inheritance ($\chi^2 = 0.41$, $df = 3$, $P > 0.5$). Neither of the three models that incorporated a major locus ($q > 0$) explained the observed segregation pattern better than the multifactorial model. H always went to zero when iterating all parameters. The complex segregation analysis of MO and MA was also performed by including only families where both parents and the other relatives were interviewed and with the transformation of data, so that relatives of unknown status were coded according to the proband's statement. These transformations did not change the outcome of the segregation analysis.

Table 3 Results of complex segregation analysis for migraine without aura (MO) (*Z* parameter takes intergenerational differences in heritability into account, *lnL* natural logarithm, *K* a constant)

Model	Heritability *(H)*	*Z*	Gene frequency *(q)*	Displacement between two homozygous means *(t)*	Degree of dominance *(d)*	$-2lnL + K$
Sporadic	0[a]	–	0[a]	–	–	−1 239.49
Multifactorial	0.77	1[a]	0[a]	–	–	−1 282.14
Multifactorial with generational difference	0.74	1.31	0[a]	–	–	−1 283.38
Recessive major locus	0[a]	1[a]	0.47	1.70	0[a]	−1 280.32
Additive major locus	0[a]	1[a]	0.10	2.95	0.5[a]	−1 281.66
Dominant major locus	0[a]	1[a]	0.084	1.61	1[a]	−1 281.33

[a] Fixed parameter

Table 4 Results of complex segregation analysis for migraine with aura (MA) (*Z* parameter that takes intergenerational differences in heritability into account, *lnL* natural logarithm, *K* a constant)

Model	Heritability *(H)*	*Z*	Gene frequency *(q)*	Displacement between two homozygous means *(t)*	Degree of dominance *(d)*	$-2lnL+K$
Sporadic	0[a]	–	0[a]	–	–	−1 236.54
Multifactorial	0.785	1[a]	0[a]	–	–	−1 312.71
Multifactorial with generational difference	0.824	0.754	0[a]	–	–	−1 313.12
Recessive major locus	0[a]	1[a]	0.34	1.92	0[a]	−1 310.44
Additive major locus	0[a]	1[a]	0.064	3.38	0.5[a]	−1 313.23
Dominant major locus	0[a]	1[a]	0.046	1.87	1[a]	−1 312.52

[a] Fixed parameter

Discussion

Results of previous studies

The inheritance of migraine is a controversial issue. The mode of transmission of unspecified migraine has been proposed to be autosomal dominant (Allen 1930; Dalsgaard-Nielsen 1965; Barolin and Sperlich 1969), autosomal recessive (Barolin and Sperlich 1969), autosomal recessive with 70% penetrance (Goodell et al. 1954), polygenic (Dalsgaard-Nielsen 1965), or multifactorial (Baier 1986). Genetic heterogeneity of liability to migraine has also been proposed (Devoto et al. 1986). The mode of transmission of MO has been suggested to be "sex-limited' (D'amico et al. 1991), multifactorial (Russell and Olesen 1993), and autosomal recessive (Mochi et al. 1993); the transmission of MA has been suggested to be multifactorial (Russell and Olesen 1993) and autosomal recessive (Mochi et al. 1993). Two of these studies include a classic segregation analysis (Devoto et al. 1986; Mochi et al. 1993). A classic segregation analysis only discriminates between different types of mendelian inheritance, and does not discriminate between mendelian inheritance and multifactorial inheritance; nor does it analyze for reduced penetrance. The different results can be explained by several factors. First, in the earlier classifications (Ad Hoc Committee of the National Institutes of Health 1962, World Federation of Neurology 1969), the diagnostic criteria for migraine were imprecise and open to individual interpretation. Furthermore, the use of a positive family history as a criterion for migraine (Ad Hoc Committee of the National Institutes of Health 1962) introduced a bias that could lead to falsely positive conclusions about the inheritance. The classification of the IHS used in the present study (Headache Classification Committee of the International Headache Society 1988) is based on operational diagnostic criteria and does not include any details about family history, with the exception of the rare subtype familial hemiplegic migraine. Second, the lack of distinction between MO and MA blurs the results of previous studies (Allen 1930; Goodell et al. 1954; Dalsgaard-Nielsen 1965; Barolin and Sperlich 1969; Baier 1985; Devoto et al. 1986), because of the high prevalence of both MO and MA (Table 2). Third, the relatives of the probands were not interviewed directly in any of the previous studies with exception of Baier 1985 and Mochi et al. 1993. This causes a tremendous bias, since values for Kappa (the chance corrected agreement rate) of the probands' familial history of MO and MA were only 0.46 and 0.42, respectively (Russell and Olesen submitted b). Fourth, probands were selected from clinical populations.

The present study

The present and previous studies (Russell and Olesen in press) did not have the methodological shortcoming mentioned above. Our study was based on probands from the general population in order to avoid the selection bias of clinical populations (Rasmussen et al. 1992). Simultaneous epidemiological studies conducted in the same area have yielded reliable prevalence rates for the background population (Rasmussen and Olesen 1992; Russell et al. 1995). All clinical examinations and interviews were carried out by one neurological research fellow (M.B.R.) in order to eliminate interobserver variability. The first degree relatives and spouses were blindly interviewed. This is important, since the diagnoses of MO and MA are based exclusively on headache history and hence are subject to bias. A more detailed discussion of the methodological considerations has been published elsewhere (Russell et al. 1995; Russell and Olesen in press). We previously found that the sex- and age-standardized population relative risk of MO was 2 and that of MA was 4 among first-degree relatives of probands with MO and MA (Russell and Olesen in press). Similarly this risk of MO was 1.5 and that of MA was 0.8 among spouses. The combined results suggest that genetic factors may be of some importance in both MO and MA. The complex segregation analysis supported this view by a significantly better fit to the multifactorial model than to the sporadic model. The results of the complex segregation analysis further suggested multifactorial inheritance of MO and MA. There was no evidence of generational difference in either type of migraine. Selection or transformation of the data did not change the outcome of the complex segregation analysis. The complex segregation analysis can not detect whether one phenotype is caused by different genotypes, i.e., genetic heterogenity. Our results therefore do not exclude that some families have a mendelian pattern of inheritance. Considering the high prevalence of MO and MA, a result indicating a single gene for either disease would have been surprising, because the gene would then be much more common than any other known disease-causing gene. Our finding of multifactorial inheritance may conceal genetic heterogeneity of MO and MA. This possibility seems likely, since familial hemiplegic migraine, a rare autosomal, dominantly inherited subtype of migraine mapping to chromosome 19 (Joutel et al. 1993) is genetically heterogeneous (Ophoff et al. 1994; Joutel et al. 1994). Four Finnish families with typical migraine were shown not to be linked to this gene (Hovatta et al. 1994). However, MO and MA were not analyzed separately in this report; this may have influenced the result, since three of the four families exhibited both types of migraine.

Our results suggest that both MO and MA have multifactorial inheritance without generational differences. This result may be explained by genetic heterogeneity of both MO and MA. Future research should be directed toward genetic linkage studies of families with a mendelian pattern of inheritance.

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Appendix A

Complex segregation analysis was performed with the computer program POINTER (Lalonet and Morton 1981). Nuclear families were distinguished according to whether or not they were ascertained through a pointer, defined as an affected person who leads to the ascertainment of a nuclear family but who is not a member of the nuclear family. Respectively, 38 and 41 nuclear families were ascertained through a parent affected by MO or MA; this provided complete selection of the possible phenotypes among the offspring (Table 1). The remaining families were ascertained through children or other relatives, resulting in incomplete selection of the possible offspring phenotypes. For both MO and MA, there was only one proband in each nuclear family, corresponding to single selection. For the purpose of the analyses, π was set to 0.001. All the parameters of the model were estimated by maximizing the overall likelihood. To test the hypotheses, the relevant parameters were held constant while estimating the remaining parameters. The value reported was $-2\ln L+K$, where $\ln L$ is the natural logarithm of the likelihood and K is a constant. The difference between the values of $-2\ln L+K$ under the general model (with m parameters) and under a reduced model (with k parameters) is asymptotically distributed as a χ^2 with $m-k$ degrees of freedom.

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