

The inheritance of migraine with aura estimated by means of structural equation modelling

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Abstract

Studies of migraine with aura (MA) have shown familial aggregation of the disorder, which cannot be explained by simple mendelian inheritance. The interest in a genetic basis for the disorder has increased after identification of three genetic loci for familial hemiplegic migraine (FHM), which is a rare subtype of MA with autosomal dominant inheritance. Both genetic and environmental factors seem to be important in the expression of MA. To elucidate the molecular pathogenesis of MA, knowledge of the relative role of genetic and environmental factors is essential. Twin studies are a classic way to analyse this. We applied structural equation modelling on MA with twin data obtained from a population based twin register in order to evaluate the effects of genes and environment. The correlation in liability of MA was 0.68 in monozygotic (MZ) and 0.22 in dizygotic (DZ) twin pairs, indicating a high degree of genetic determination in the total variance of liability. The best fitting model combined additive genetic effects and environmental effects that were not shared by the twins. The estimate of heritability was 0.65 and similar in males and females.

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Migraine with aura (MA, formerly classical migraine) is a common neurological disorder with age at onset before 40 years in the majority of cases.^{1,2} Attacks are characterised by an initial aura, that is, reversible visual, sensory, aphasic, or motor symptoms usually lasting less than 60 minutes, and followed by a headache.³ The attacks may be accompanied by nausea, photophobia, and phonophobia.³ Familial hemiplegic migraine (FHM) is a rare subtype of MA with autosomal dominant inheritance. The discovery that FHM is a genetically heterogeneous disorder with at least three different loci⁴⁻⁷ has stimulated the search for a genetic basis of MA.

Studies of families with MA have suggested a familial susceptibility in the aetiology,^{8,9} which does not follow simple mendelian inheritance. An analysis of 31 high risk families with affected subjects in more than one generation found that autosomal dominant inheritance with reduced penetrance was unlikely even in these families.¹⁰

Autosomal recessive inheritance is unlikely because of the unequal sex distribution, females being more often affected than males.^{1,2,11} However, the female preponderance is too low to suggest sex influenced inheritance.¹⁰ Mitochondrial and X linked inheritance may occur in subgroups of affected subjects, but are excluded in many families because of paternal transmission.

MA is likely to be caused by interactions of genetic and environmental factors. A complex segregation analysis of 127 probands and their first degree relatives from the general population indicated multifactorial inheritance without generational differences.¹² Studies of twins may help to clarify the relative importance of genetic and environmental factors. A recent twin study has emphasised the importance of genetic factors, since monozygotic (MZ) twin pairs had significantly higher concordance than dizygotic (DZ) twin pairs.¹³

We applied structural equation modelling on MA with twin data obtained from a population based twin register, thereby evaluating the influence of genetic and environmental factors and providing a quantitative estimate of the heritability.

Materials and methods

SAMPLING

The study population originated from the population based Danish Twin Register which is representative of Danish twins.¹⁴ Twins born between 1953 and 1960 were included and comprised 2026 MZ and 3334 same sex DZ twins. A total of 87% of the twins completed a screening questionnaire about migraine.¹⁵ The level of ascertainment was 85%.¹³ All twin pairs with at least one twin who had self-reported migraine or self-reported severe headache with accompanying symptoms were interviewed by one of two neurological residents experienced in headache diagnosis (VU, MG). The participation rate in the telephone interview was 90%.¹³ The criteria of the International Headache Society were used.³ A more detailed description of the study design and methods has been given elsewhere.¹³

STATISTICAL ANALYSIS

The structural equation modelling approach is based on a classical biometric analysis of data. The underlying assumption is that the variance of a quantitative phenotype can be broken down into two components, the genotypic variance and the environmental variance.¹⁵ The genotypic variance can be subdivided into the variance owing to additive genetic effects (A)

Table 1 The number of concordant, discordant monozygotic (MZ), and same sex dizygotic (DZ) twin pairs. Proband concordance rates and correlations in liability with 95% confidence intervals. Lifetime prevalence of migraine with aura in percentage

	Males		Females		Overall	
	MZ	DZ	MZ	DZ	MZ	DZ
No of pairs						
Concordant	12	10	14	6	26	16
Discordant	21	48	30	70	51	118
Proband concordance rate	0.53 (0.35-0.71)	0.29 (0.15-0.43)	0.48 (0.32-0.64)	0.15 (0.04-0.26)	0.50 (0.38-0.62)	0.21 (0.12-0.30)
Correlation in liability	0.71 (0.50-0.92)	0.32 (0.05-0.59)	0.66 (0.46-0.86)	0.11 (0.01-0.38)	0.68 (0.54-0.82)	0.22 (0.03-0.41)
Lifetime prevalence	6.8		7.8		7.1	

Table 2 Model fitting on migraine with aura by combining effects in genetic variance and effects in environmental variance

	Genetic effects		Environmental effects		Goodness of fit tests			
	Additive	Non-additive	Shared	Non-shared	χ^2	df	p	AIC†
	A	D	C	E				
Males								
ACE	0.70 (0.07-0.86)	—	0.00 (0.00-0.48)	0.30 (0.14-0.53)	1.58	2	0.45	-2.42
ADE	0.59 (0.00-0.86)	0.12 (0.00-0.86)	—	0.29 (0.13-0.53)	1.54	2	0.46	-2.46
AE*	0.70 (0.47-0.86)	—	—	0.30 (0.14-0.53)	1.58	3	0.66	-4.42
CE	—	—	0.00 (0.00-0.00)	1.00 (0.24-1.00)	29.28	3	0.00	23.28
E	—	—	—	1.00 (1.00-1.00)	29.28	4	0.00	21.28
Females								
ACE	0.60 (0.23-0.78)	—	0.00 (0.00-0.00)	0.40 (0.22-0.63)	9.30	2	0.01	5.30
ADE	0.00 (0.00-0.00)	0.65 (0.00-0.82)	—	0.35 (0.18-0.57)	7.03	2	0.03	3.03
AE*	0.60 (0.37-0.78)	—	—	0.40 (0.22-0.63)	9.30	3	0.03	3.30
CE	—	—	0.38 (0.19-0.54)	0.62 (0.46-0.81)	16.74	3	0.00	10.74
E	—	—	—	1.00 (1.00-1.00)	32.08	4	0.00	24.08
Overall								
ACE	0.65 (0.36-0.78)	—	0.00 (0.00-0.00)	0.35 (0.22-0.51)	3.23	2	0.20	-0.77
ADE	0.21 (0.00-0.75)	0.48 (0.00-0.81)	—	0.32 (0.19-0.48)	1.84	2	0.40	-2.16
AE*	0.65 (0.49-0.78)	—	—	0.35 (0.22-0.51)	3.23	3	0.36	-2.77
CE	—	—	0.44 (0.31-0.56)	0.56 (0.44-0.69)	15.46	3	0.00	9.46
E	—	—	—	1.00 (1.00-1.00)	54.22	4	0.00	46.2

95% confidence intervals in parentheses.

* Best fitting model by AIC.

† Akaike's information criterion.

and the variance owing to non-additive genetic effects (D).¹⁵ The additive genetic effects are the effects of genes taken singly and added over multiple loci. The non-additive genetic effects are the effects of intralocus gene interactions. Correspondingly, the environmental variance is divided into effects shared by subjects (C) and effects not shared by subjects (E).¹⁵ The shared environmental effects contribute to the subjects' phenotypic similarity and the non-shared environmental effects contribute to the subjects' dissimilarity. The model fit is assessed by combining the various parameters A, C, D, and E. Possible models are ACE, ADE, AE, CE, and a model with E as the single parameter. The effects of additive genetic effects A and shared environmental effects C cannot be combined,¹⁶ leaving the ACE model a theoretical possibility. The criteria for best fitting model was Akaike's information criterion (AIC) which combines the goodness of fit χ^2 with degrees of freedom.¹⁶ The model with the lowest value of AIC is considered to have the best fit.¹⁶

Heritability in the broad sense is defined as the proportion of the total variance owing to the genetic variance and is a quantitative measure.¹⁵ To estimate the different components of the total variance for a non-quantitative trait like MA by means of structural equation modelling, it is assumed that there is an underlying normally distributed liability to MA. The concept of liability implies a graded continuum of unmeasured, continuously distributed latent traits.^{15 17} A high degree

of correlation of liability between MZ twins expresses a high degree of genetic determination of the total variance in liability to a disease. The correlations of liability are calculated for MZ and DZ twins by means of the probandwise concordance rates and the lifetime prevalence of MA. The probandwise concordance rate is the proportion of affected twin partners of probands in relation to the total number of affected twins.¹⁶

The structural equation modelling was performed by means of the MX software computer program.

Results

A total of 211 twin pairs (77 MZ, 134 DZ) were identified.¹³ The number of concordant pairs was 42 (26 MZ, 16 DZ) and the number of discordant pairs was 169 (51 MZ, 118 DZ).¹³ The probandwise concordance rates, the correlations in liability, and the lifetime prevalence of MA are shown in table 1. The results of the structural equation modelling are shown in table 2. The best fitting model was an AE model including additive genetic effects and environmental factors that were not shared by the twins. This was also the best fitting model for males analysed separately. In females, both an AE model with additive genetic effects and non-shared environmental effects, and an ADE model with dominant genetic effects and non-shared environmental effects, fitted the data. The heritability estimate was 0.65 under the AE model.

Discussion

Our results can be considered representative since the ascertainment of twins was optimal.^{13 14} Only twins born between 1953 and 1960 were included since MA usually occurs before the age of 40 years.^{1 2} The probandwise concordance rate was significantly higher in MZ than in DZ twin pairs which emphasises that genetic factors are indeed important in the aetiology of MA. The correlation of liability was 0.68 in MZ twin pairs with no significant difference between males and females. This indicates a high degree of genetic determination of MA in the total variance in liability. The correlation of liability was higher in MZ twin pairs than in DZ twin pairs, as expected.

The best fitting model was the AE model which combines additive genetic effects and effects of environment that are not shared by the twins. The ADE model including both dominant genetic and additive genetic effects in combination with non-shared effects of environment also fitted the data in females, while in males the AE model had a better fit than the ADE model. In females the ADE model included dominant genetic effects only. However, a model including dominant genetic effects tends to have additive genetic effects.¹⁵ Furthermore, the estimate of the non-additive genetic effects had very wide confidence intervals, which makes it difficult to separate the effects. The ADE model is thus unlikely in females and only suitable from a theoretical point of view. The models totally excluding genetic effects fitted the data poorly. In the ACE model including additive genetic effects and effects of environment, only the environmental effects that were not shared by the twins counted, since additive genetic effects and shared environmental effects are impossible to separate.¹⁶ The proportion of the non-shared effects in the ACE model was similar to the proportion of non-shared effects of environment in the ADE and AE models. Thus, the total effect of the environmental variance was constant and accounted for approximately 0.35 of the total variance, and included only non-shared effects. Correspondingly, the total effect of the genetic variance, that is, the heritability, is considered constant amounting to

approximately 0.65 of the total variance, although the proportion of additive genetic and dominant genetic effects may vary. Our heritability estimate is in accordance with the estimate of 0.79 in a complex segregation analysis of 127 families with MA from the general population.¹²

Our results indicate that the liability to MA has a high degree of genetic determination and that the phenotypic variation is a combination of genetic and individual specific environmental factors.

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