CHAPTER 11

SHARED GENETIC FACTORS IN MIGRAINE AND DEPRESSION: EVIDENCE FROM A GENETIC ISOLATE

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ABSTRACT

Objective: To investigate the co-occurrence of migraine and depression and assess whether shared genetic factors may underlie both diseases.

Methods: Subjects were 2,652 participants of the Erasmus Rucphen Family (ERF) genetic isolate study. Migraine was diagnosed using a validated three-stage screening method that included a telephone interview. Symptoms of depression were assessed using the Centre for Epidemiologic Studies Depression (CES-D) scale and the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D). The contribution of shared genetic factors in migraine and depression was investigated by comparing heritability estimates for migraine with and without adjustment for symptoms of depression, and by comparison of the heritability scores of depression between migraineurs and controls.

Results: We identified 360 migraine cases, 209 had migraine without aura (MO) and 151 had migraine with aura (MA). Odds ratios for depression in migraine patients were 1.29 (95% confidence interval (CI) 0.98-1.70) for MO and 1.70 (95% CI 1.28-2.24) for MA. Heritability estimates were significant for all migraine (0.56), MO (0.77), and MA (0.96), and decreased after adjustment for symptoms of depression or use of antidepressant medication, in particular for MA. Comparison of the heritability scores for depression between migraine patients and controls showed a genetic correlation between the HADS-D score and MA.

Conclusions: There is a bidirectional association between depression and migraine, in particular MA, which can be explained, at least partly, by shared genetic factors.

INTRODUCTION

Migraine is a highly prevalent brain disorder that is characterized by recurrent headache attacks associated with nausea, vomiting, photo- and phonophobia (migraine without aura; MO). In one third of migraineurs, attacks are preceded by transient focal neurological symptoms (migraine with aura; MA).[1] Migraineurs often have symptoms of depression. Population-based odds ratios (OR) range from 2.0 to 5.8, with strongest associations for MA.[2-13] The quality of life of migraineurs with depression is decreased.[10,14] Co-morbid depression is a risk factor for chronification of migraine[15-17] and development of medication–overuse-headache.[18] Patients with depression also have an increased risk for migraine, with risk estimates of 2.8-3.4 for migraine, 2.2 for MO and 4.0 for MA.[2-4] This bidirectional relationship suggests that migraine and depression may share common etiological factors.

Twin- and family-based studies have shown that both migraine and depression have a strong genetic basis.[19-24] Heritability estimates range from 0.33-0.53 for migraine (33-53% of the trait is explained by additive genetic effects) to 0.61-0.77 for MO and 0.65-0.79 for MA.[19-23] For depression, heritability estimates range from 0.17-0.78.[24] Recent evidence suggests that both diseases share molecular pathways controlling serotonergic and glutaminergic neurotransmitter systems.[25,26] Shared genetic factors may therefore underlie the bidirectional comorbidity of migraine and depression.

Here we determined the co-occurrence of migraine and depression in a Dutch genetic isolate, investigated to what extent genetic factors are involved in migraine, and whether shared genetic factors may underlie the comorbidity of both disorders.

METHODS

Study Population

Subjects were participants of the Erasmus Rucphen Family (ERF) study, a family-based study in a genetically isolated community in the Southwest of the Netherlands.[27] In brief, the ERF study population includes 3,465 individuals that were ascertained based on genealogical background (not selected on phenotypes of interest), and are living descendants of 22 couples with at least six children baptized in the community church between 1850 and 1900. Founding couples are related through previous generations as demonstrated by extensive genealogical information from detailed church and municipal records. Hence, study participants were all members of a large extended pedigree. All individuals of 18 years and older were invited to participate. Spouses were invited only for family members that had children of 18 years and older.

Standard Protocol Approvals, Registrations, and Patients

The study was approved by the Medical Ethical Committee of the Erasmus MC Rotterdam and all participants gave written informed consent.

Clinical evaluation

Extensive clinical information from ERF participants (n = 3,465) was available.[27] For this study relevant clinical data were obtained by questionnaires (symptoms of headache and depression and education level) or from a visit to the research centre (use of antidepressant medication).

Migraine

Migraineurs were identified between 2005 and 2007 using a three-stage screening procedure assessing lifetime occurrence of migraine, which was previously validated in a population-based study[28] and which was based on the Classification Criteria of the International Headache Society (IHS).[1] In brief, in the first stage, participants were asked to fill in five screening questions on headache and aura symptoms. Then, screen-positives received a detailed questionnaire on headache and aura symptoms. Finally, screen-positives were interviewed by telephone for further clarification of their answers. Subjects that were screen-positive but did not return the extensive headache questionnaire and subjects that could not be screened because they did not, or incompletely, filled in the screening questions, were directly contacted by telephone. Telephone interviews were performed by the principal study physician (AHS), who is experienced in diagnosing migraine patients, and by well-trained medical students supervised by AHS. A final diagnosis was only made after the telephone interview and in consultation with a neurologist specialized in headache (GMT).

Depressive symptoms

Symptoms of depression were assessed using the Centre for Epidemiological Studies Depression Scale (CES-D)[29] and the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D).[30] Both scales are validated, reliable self-report measures of symptoms of depression.[31, 32] The CES-D consists of 20 items with total scores ranging from 0 to 60 and the HADS-D of seven items with scores ranging from 0 to 21. Higher scores indicate more symptoms of depression. Depression scores were analyzed both as continuous variables and as dichotomous variables. For the dichotomous variable, depression was defined as a CES-D score ≥ 16[31] and HADS-D score ≥ 8[32] or the use of antidepressant medication. CES-D scores were missing for 327 and HADS-D for 104 subjects. Missing CES-D and HADS-D data were imputed based on data of the other depression scale, age, sex and use of antidepressants using SPSS version 12.0, iterative expectation-maximization method. Depression scores were not imputed when both scores were missing.

Control group

The control group consisted of subjects that: (i) did not report severe headache (pain severity score ≤ 4 on a scale from 0 to 10); ii) did not report visual aura symptoms; (iii) had never been diagnosed with migraine by a physician; and (iv) never used specific anti-migraine medication. Thus, also subjects with mild headache in combination with visual aura are excluded from the control group. To exclude false negative control cases, we used an even more conservative definition for a non-migraineurs than in our previous population-based study.[28]

Statistical methods

For statistical analysis we used data from three migraine groups (i.e., all migraine cases, MO, and MA) and the control group. General characteristics of the subjects of each group were compared using chi-square statistics for dichotomous variables and a Student's t-test for continuous variables.

All analyses were corrected for inbreeding. The coefficient of inbreeding per individual was calculated based on available genealogical information using PEDIG software.[33] This coefficient reflects the probability that two alleles at a given locus in an individual are identical by descent.

To examine the co-occurrence of migraine and depression, we calculated the odds ratio (OR) for the risk of depression for each migraine group using multivariate mixed model regression analyses corrected for inbreeding, age, sex and education and taking into account pedigree relations between individuals (polygenic liability threshold model).[34]

Mean CES-D and HADS-D scores were calculated for each group. *P*-values comparing migraine subgroups versus controls were corrected for age, sex, level of education, use of antidepressants, inbreeding and pedigree relations by multivariate linear mixed model regression, considering each migraine group as an independent variable and HADS-D or CES-D data as the continuous dependent variable. Because both CES-D data and HADS-D data deviated from the normal distribution, data were transformed by taking the natural logarithm (CES-D) and by taking the square root (HADS-D).

We calculated the heritability estimates (h^2) as the ratio of the variance of a trait that is explained by additive polygenic effects to total phenotypic variance of the trait. The polygenic model was applied that assumes an infinite number of genetic factors with a small additive effect contributing to the trait variance. Analyses were adjusted for age, sex and inbreeding. As sibship effects, a combination of effects induced by sharing early childhood environment and dominant genetic variation, did not significantly influence heritability estimation, this covariate was excluded from the analyses.

Involvement of shared genetic factors underlying migraine and depression was assessed by two complementary methods. First, heritability estimates for migraine were computed with and without depressive symptoms as covariate (i.e., HADS-D, CES-D scores and use of antidepressants included) (see also[27]). A difference between adjusted and unadjusted heritability estimates represents that part of the genetic component in migraine that is shared with depression.

Second, we compared the heritability of depression in migraine patients to that in controls (i.e., assess whether a diagnosis of migraine influences the heritability of depression) by performing a bivariate polygenic analysis with both HADS-D and CES-D scores (i.e., depression score + migraine status, covariates: age, sex, inbreeding, use of antidepressant medication) (see for examples[35,36] except here, we compared migraine versus no migraine status, instead of gender, to estimate the genetic correlation). The significance of a genetic correlation was determined using a likelihood ratio test.

Descriptive analyses were performed using SPSS version 12.0 for windows (SPSS, Chicago, IL). SOLAR 2.1.2 software package (Southwest Foundation for Biomedical Research, San Antonio, Texas, USA) was used for calculation of heritability estimates, regression analyses and genetic correlations.

RESULTS

Recruitment of migraine patients

In total, 3,465 subjects participated in the ERF study. Figure 1 shows the ascertainment flow chart of migraine cases. The questionnaire with headache screening questions was returned by 2,652 (76.5%) subjects. Of these, 888 were screen-positive and 1,291 screen-negative; 473 subjects had not or only incompletely, filled out the screening questionnaire. Of the screen-positives, 572 (64.4%) subjects could be interviewed of which 305 proved to have migraine. Of the group that was incompletely screened, 286 (60.5%) subjects were interviewed of which 55 proved to have migraine. A diagnosis could not be made in 503 subjects because of a variety of mainly logistic reasons. Of the in total 2,149 ERF participants who were interviewed (n=858) or who were screen-negative (n=1291), 360 (16.8 %) had migraine. Of these, 209 (58%) had MO and 151 (42%) had MA. A total of 617 subjects gave negative answers to all screening questions, thereby fulfilling the criteria for the control group.

Descriptive data

The demographic characteristics of all groups are shown in Table 1. No significant differences were found for the mean age. In line with the higher prevalence of migraine in women, more

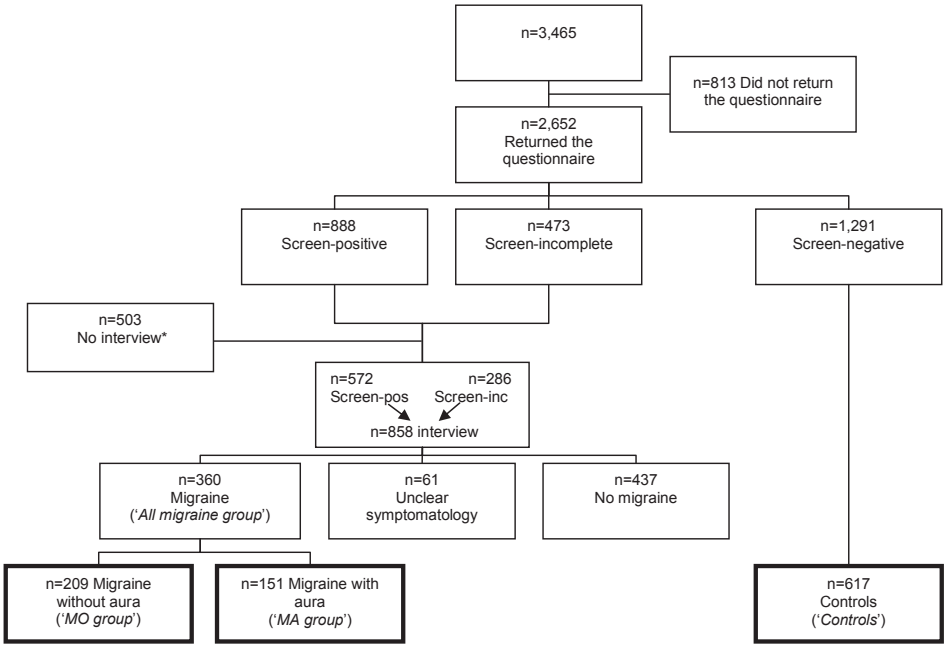

Figure 1. Flowchart of ascertainment of migraine cases and the controls in the Erasmus Rucphen Family study
* Subjects were deceased or declined participation (n=122), had an incorrect (n=140) or unavailable (n=10) telephone number, gave no permission for a telephone interview (n=130), were not answering the phone (at least 3 attempts were made) (n=72) or indicated on the phone that they did not want to cooperate with the interview (n=29).

Table 1. Distribution of sex, age, and education in the various groups

Characteristics	All migraine (n=360)	MO (n=209)	MA (n=151)	Controls (n=617)
Women, %	75*	77*	73*	47
Mean age in years (SD)	46.2 (12.3)	47.0 (12.7)	45.1 (11.6)	47.8 (15.3)
Education, %				
Higher	5§	5	4§	9
Medium	64	63	66	65
Lower	31	32	30	26

MO: migraine without aura; MA: migraine with aura. Education: Higher: college or university, Medium: secondary school or vocational technical training, Lower : primary or elementary school or unfinished secondary school. *$p < 0.001$ compared to controls; §$p < 0.05$ compared to controls. SD: standard deviation.

women were present in the migraine groups. Overall, patients with migraine, in particular those with MA, had a lower education than controls.

Depression in migraineurs

Of the 2,652 participants that completed the questionnaire, HADS-D scores were obtained for 2,548 subjects and CES-D scores for 2,325. After imputation, HADS-D and CES-D scores were available for 2,584 subjects. Of these, 583 met our definition for depression. Of these, 91 were included in the migraine group and 82 in the non-migraine control group. The remaining subjects were not included in the current assessment because they did not meet the inclusion criteria for either the all migraine or control group.

Twenty-five percent (91/360) of migraineurs and 13% (82/617) of controls were found to be depressed (Table 2). Depression was more often seen in MA (32%; 48/151) than in MO (21%; 43/209). The ORs were 1.43 (95% CI 1.15 -1.78) for all migraine, 1.29 (95% CI 0.98-1.70) for MO, and 1.70 (95% CI 1.28-2.24) for MA. Mean CES-D scores were higher ($p < 0.001$) in migraine patients compared to controls (all migraine: 12.0 ± 10.2, MO: 11.1 ± 9.7, MA: 13.2 ± 10.7, and controls: 7.5 ± 7.4). The mean HADS-D score was higher ($p < 0.01$) in the all migraine and MA groups compared to controls (all migraine: 6.1 ± 4.4 and MA: 6.7 ± 4.6), but was not significantly different between the MO and control group (MO: 5.7 ± 4.2 and controls: 4.9 ± 3.7).

Table 2. Depression in migraine patients and controls

Group	Depression (n, (%))	OR (95% CI)	*p* value
Controls (n=617)	82 (13%)	1.00	-
MO (n=209)	43 (21%)	1.29 (0.98-1.70)	0.07
MA (n=151)	48 (32%)	1.70 (1.28-2.24)	< 0.001

MO: migraine without aura; MA: migraine with aura. Prevalence of depression per group is given. Depression was defined as scoring both CES-D ≥ 16 and HADS-D ≥ 8 or use of antidepressants. Odds ratios for the risk of depression in migraine patients are adjusted for sex, age, education and inbreeding.

Heritability estimates of migraine

In total 325 migraine patients (188 MO and 137 MA) and 562 control subjects were present in the ERF extended pedigree.[27] Heritability estimates were 0.56 (95% CI 0.26-0.86) for all migraine, 0.77 (95% CI 0.38-1.00) for MO, and 0.96 (95% CI 0.51-1.00) for MA (Table 3). These estimates decreased after adjustment for depressive symptoms to 0.51 (95% CI 0.19-0.83) for all migraine, 0.75 (95% CI 0.32-1.00) for MO, and 0.81 (95% CI 0.31-1.00) for MA. The decrease was highest in patients with MA (15%), compared to a decrease of 4% in the all migraine group and 2% in MO patients. This would suggest that shared genetic factors particularly underlie the comorbidity of depression and MA.

Table 3. Heritability estimates of migraine with and without adjustment for depression

	h^2 (95% CI)[a]	h^2 (95% CI) (with adjustment for depression)[b]	*p* value[c]
All migraine (n=325)	0.56 (0.26-0.86) **	0.51 (0.19-0.83) **	0.81
MO (n=188)	0.77 (0.38-1.00) **	0.75 (0.32-1.00) **	0.95
MA (n=137)	0.96 (0.51-1.00) **	0.81 (0.31-1.00) *	0.65

MO: migraine without aura; MA: migraine with aura. [a]Heritability estimates are based on a polygenic model, covariates: age, sex and inbreeding coefficient. [b]Heritability estimates are based on a polygenic model, covariates: age, sex and inbreeding coefficient, HADS-D, CES-D, use of antidepressant medication. [c]P value for the difference in heritability estimates before and after adjustment for depression. *P* values for heritability estimates: **p <0.001 and *p <0.01.

Next we compared the heritability for depression in migraineurs and controls. A correlation of 1 indicates that there is no difference in the genetics of depression between patients and controls, while a deviation from 1 suggests shared genetic factors for depression and migraine. Only for HADS-D and MA a reduced genetic correlation was found (correlation of 0.36) indicating that genetic factors causing symptoms of depression in MA patients differ to those involved in depression in controls. In MO patients the correlation coefficient was 1 indicating no difference in genetic factors for depression in MO and controls. For CESD there was no difference seen between migraine patients and controls.

DISCUSSION

We investigated the co-occurrence of migraine and depression in a large Dutch genetic isolate and to what extent shared genetic factors are involved. Our study is particularly suited to address these questions because of the following reasons: (i) our three-step diagnostic procedure - including a telephone interview for clarification and confirmation of the clinical symptoms and a final diagnosis according to the Classification Criteria of the IHS[1] guaranteed a highly reliable diagnosis of migraine; (ii) the presence of depression was assessed using two different depression scales; (iii) our study population includes a very large number of well-characterized subjects covering a broad age range from 18 to 91 years.

We found an increased risk of depression and depressive symptoms in migraine patients, in particular in those with aura. These findings are in agreement with previous studies from outbred populations.[2-13] ORs for depression in migraine patients in those studies were larger (2.0 – 5.8 for MA) than ORs observed here (1.7 for MA), which may be due to differences in the diagnostic methods, and definitions. This seems particularly true for depression. While several studies addressed *life-time* prevalence of depression,[2,4,5,9] which is notoriously difficult to assess reliably, we studied *current* depression, which is reliable to diagnose and will result in lower prevalence data. One might thus argue that presence of lifetime depression was underestimated in our study.

Some 23.5% of the 3,465 subjects were non-responders, which may have introduced a selection bias leading to an overrepresentation of very depressed patients or severe migraine patients in the non-responder population. However, such a bias in this particular study is less likely, as we used a general questionnaire designed to collect information on a large number of traits, not only related to headache and depression.

Heritability estimates in our study were significant for all three migraine groups and were substantially higher for MA than for MO. This is in accordance with studies in outbred populations,[19-23] confirming the hypothesis that the genetic contribution in MA is stronger than in MO. Also in line with these studies, a lower heritability estimate was observed for 'all migraine' than for MO or MA, which indicates that MA and MO share some, but not all, genetic factors. We observed a remarkably high heritability for MA of over 90% in ERF. This suggests that most of the variance in MA in ERF is explained by genetic factors. This finding may be particularly relevant for gene discovery and suggests that MA is the most promising migraine subtype to search for migraine genes. Moreover, our observation that heritability estimates for MA decreased when adjusting for depression, indicates that *shared* genetic factors may underlie depression and MA. For MO, a smaller decrease in heritability estimates was observed, suggesting that a small fraction of the comorbidity with depression is explained by shared genetic factors for this migraine subtype.

In our bivariate analysis, we found remarkably different results when using the two depression scales. When depression was determined by using the HADS-D scale, we found evidence for shared genetic factors for migraine with aura and depression. However, no such association was observed when depression was determined using the CES-D scale. This discrepancy may seem remarkable as both scales have been validated for the assessment of symptoms of depression[31,32] and there is a high correlation for both depression scales in our study (Pearson correlation coefficient rho = 0.75; $p < 0.001$). However, both scales assess slightly different symptoms, which may well explain our findings. As the HADS-D was specifically designed to prevent noise signal from somatic disorders,[32] it excludes 'physical symptoms' of depression, such as insomnia, fatigue or loss of appetite. In the CES-D scale, however, these symptoms are included. Although admittedly difficult to prove, we would like to argue that these physical symptoms are more likely a consequence of the migraine attacks than due to a depression. Consequently, we propose that the CES-D score, in a way, is confounded by migraine-related symptoms and therefore less suited to assess shared genetic factors in migraine and depression.

Previous studies found a bidirectional association between migraine, in particular those with aura, and depression.[2-4] This suggests that common pathogenetic pathways, at least partly, underlie both disorders, rather than that one is the consequence of the other. Thus, migraine patients may develop depression as a result of the demoralizing experience of recurrent and disabling headaches. However, then a correlation with disease disability would be expected, which was not found in previous studies.[2] Also, an even stronger association with MO should be seen, which in general is the more disabling form of migraine[1] and usually associated with higher attack frequencies. Our study provides evidence that this bidirectional relationship can be explained, at least partly, by shared underlying genetically determined disease mechanisms. Support for our findings comes from a recent twin study that also suggested that shared genetic risk factors may underlie migraine and depression.[37] Unfortunately that study has important limitations. First of all, it is unclear whether a correct migraine diagnosis was made as a diagnosis was based on 'self-reported physician's diagnosis', and not on well-defined IHS criteria. A similar criticism can be made with respect to the diagnosis of depression. This may well have led to misclassification and underreporting of migraine and depression. Second, unlike in our study, the sample consisted of female subjects only, and results therefore cannot be extrapolated to male patients. Third, no distinction was made between MA and MO. This last limitation is very relevant in light of our observation that shared genetic effects between migraine and depression are particular evident for migraine with aura.

Identification of common genetic factors may significantly improve the insight into the molecular basis of these common and highly disabling episodic brain disorders.

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