Increased familial risk and evidence of genetic factor in migraine

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Abstract

Objective—To investigate familial occurrence of migraine with and without aura.

Design—Familial occurrence of migraine with and without aura among first degree relatives and spouses of probands with migraine with or without aura and those who had never had migraine. All interviews of first degree relatives and spouses were done blindly by a neurological resident. The operational diagnostic criteria of the International Headache Society were used.

Setting—General population from Copenhagen County.

Subjects—The 378 probands had 1109 first degree relatives and 229 spouses.

Main outcome measures—Patterns of familial aggregation of migraine with and without aura as assessed by calculation of the population relative risk.

Results—Compared with the general population the first degree relatives of probands with migraine without aura had 1·9 times the risk of migraine without aura and 1·4 times the risk of migraine with aura. The first degree relatives of probands with migraine with aura had nearly four times the risk of migraine with aura and no increased risk of migraine without aura. The first degree relatives of probands who had never had migraine had no increased risk of migraine either with or without aura. Spouses of probands with migraine without aura had 1·4 times the risk of migraine without aura whereas spouses of probands with migraine with aura had no increased risk of migraine with aura.

Conclusion—The different familial patterns indicate that migraine without aura and migraine with aura have a different aetiology. Migraine without aura seems to be caused by a combination of genetic and environmental factors whereas migraine with aura is probably determined largely or exclusively by genetic factors.

Introduction

A gene for familial hemiplegic migraine, a rare autosomal dominant inherited subtype of migraine, was recently mapped to chromosome 19.[1] This has spurred interest in the possible genetic background of the common types of migraine—migraine without aura (previously known as common migraine) and migraine with aura (previously known as classic migraine). Unfortunately it is much less clear if these types of migraine are inherited. Previous family studies have suggested a genetic factor based on a frequent family history of migraine.[2-13] The 16-21% prevalence of migraine in the general population, however, may cause this simply by chance.[14,15] The family studies also have several shortcomings. Most important are the lack of direct interview of relatives,[2-13] selection of clinic populations,[2-13] and lack of distinction between types of migraine.[2-10,12] More valid is the genetic-epidemiological approach used in two previous studies.[16,17] The first study found that first degree relatives of probands with migraine had a non-significant increased risk of migraine compared with first degree relatives of probands with no migraine.[16] In the second study first degree relatives of probands with migraine without aura had three times the risk of migraine without aura, and first degree relatives of probands with migraine with aura had twice the risk of migraine with aura compared with the general population.[17] The genetic epidemiological studies, however, also suffer from lack of direct interview of relatives. Therefore it remains uncertain whether there is a significant familial occurrence of migraine with and without aura and if so whether this is due to genetic or environmental factors.

We determined the prevalence and relative risk of migraine with and without aura in first degree relatives of probands with migraine without aura, with migraine with aura, and who had never had migraine. The risk of migraine with and without aura in spouses was used to elucidate the relative role of genetic and environmental factors, as probands and spouses in part share their environment but differ in genetic constitution.

Subjects and methods

DATA COLLECTION

A sample of 3000 men and 1000 women aged 40 years was drawn from the Danish Central Person Registry.[15] The probands were found among this study population. All people with migraine with aura were included as probands. An equivalent number of probands with migraine without aura was randomly selected. Similarly, probands who had never had migraine were selected as a random sample of people without self reported migraine.[15] All those with co-occurrence of the two types of migraine were included as probands. The probands supplied information about their spouse and first degree relatives age 18 years or above. Spouses of probands who had never had migraine were included only if the proband and spouse had a child or children age 18 or above. The spouses and first degree relatives were interviewed by telephone. Their relation to the probands was blinded for the interviewer (MBR). The operational diagnostic criteria of the International Headache Society were used.[18]

Some probands did not allow interview of their family: 3% (4/132) of probands with migraine without aura, 6% (8/137) of probands with migraine with aura, 11% (2/19) of probands with co-occurrence of migraine with and without aura, and 11% (13/122) of probands who had never had migraine. No significant differences regarding migraine reported by the probands were found between families interviewed and those not interviewed. Five probands (four adoptees and one without living relatives) were not included. Only spouses and first degree relatives interviewed were included in the analyses. The participation rate was high among those it was possible to contact; 94% (229/244) of spouses and 93% (1109/1190) of first degree relatives were interviewed.

A total of 48 spouses were not interviewed; reasons were death (three), alcoholism (one), unknown address (17), contact was impossible to obtain (11), there was no telephone and no reply to a standard letter asking for calling back (two), contact of the spouse not allowed by the proband (12), and the spouse declined to participate (two). A total of 460 first degree relatives

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were not interviewed. The primary reason was death (252). Other reasons were dementia (11), mental retardation (four), insanity (three), alcoholism (one), unknown parent (16), unknown address (56), contact impossible to obtain (41), no telephone and no reply to a standard letter asking for calling back (27), contact with certain first degree relatives not allowed by the proband (36), and the first degree relative declined to participate (13). No significant differences were found between the first degree relatives interviewed and those not interviewed regarding migraine reported by probands. Significantly more male than female first degree relatives were not interviewed (161/691 v 91/670; $P<0.001$). The project was approved by the Danish ethics committees.

STATISTICAL METHODS

The prevalences of migraine with and without aura among first degree relatives were estimated by dividing the number of relatives with either condition by the number of first degree relatives.

TABLE I—*Sex and age specific prevalence of migraine with and without aura per 1000 inhabitants*[15]

Age (years)	Migraine with aura		Migraine without aura	
	Males	Females	Males	Females
0-9	9	16	27	18
10-19	39	47	60	110
20-29	51	63	85	177
30-39	63	96	93	201
≥40*	69	106	102	221
Overall prevalence	55	82	83	177

*Prevalence estimated to be 10% higher than in the age group 30-39.[1 22]

TABLE II—*Family history of migraine with and without aura in the different groups of probands. Values in parentheses are numbers of men and women*

			No of affected first degree relatives	
Disease in proband	No of probands	No of first degree relatives	Migraine with aura	Migraine without aura
Migraine without aura	126 (73 m, 53 f)	354	42	102
Migraine with aura	127 (76 m, 51 f)	359	111	56
Both types of migraine	17 (9 m, 8 f)	59	11	16
Never had migraine	108 (60 m, 48 f)	337	18	58

TABLE III—*Prevalence (95% confidence interval) of migraine with and without aura per 1000 first degree relatives*[1]

	Prevalence among first degree relatives	
Disease in proband	Migraine with aura	Migraine without aura
Migraine without aura	118 (84 to 151)	285 (239 to 331)
Migraine with aura	308 (260 to 356)	155 (118 to 192)
Both types of migraine	176 (80 to 273)	246 (141 to 350)
Never had migraine	52 (29 to 75)	168 (130 to 207)

*Prevalences for general population are shown in table I.

TABLE IV—*Sex and age standardised risk of migraine with and without aura among first degree relatives and spouses in different groups of probands*

Disease in proband	Disease in first degree relative/spouse	No affected		Population relative risk* (estimated 95% confidence interval)
		Observed	Expected	
	Relatives			
Migraine without aura	Migraine without aura	102	54·84	1·86 (1·56 to 2·16)
	Migraine with aura	42	29·17	1·44 (1·03 to 1·85)
Migraine with aura	Migraine without aura	56	55·10	1·02 (0·77 to 1·26)
	Migraine with aura	111	29·26	3·79 (3·21 to 4·38)
Co-occurrence of migraine with and without aura	Migraine without aura	16	9·77	1·64 (0·94 to 2·33)
	Migraine with aura	11	5·07	2·17 (0·98 to 3·36)
Never had migraine	Migraine without aura	58	52·41	1·11 (0·83 to 1·39)
	Migraine with aura	18	27·73	0·65 (0·36 to 0·94)
	Spouses			
Migraine without aura	Migraine without aura	26	16·85	1·54 (1·03 to 2·06)
	Migraine with aura	6	9·24	0·65 (0·14 to 1·15)
Migraine with aura	Migraine without aura	22	15·45	1·42 (0·89 to 1·96)
	Migraine with aura	6	8·01	0·75 (0·30 to 1·20)

*Observed number of affected relatives divided by expected number.

The risk of familial occurrence was assessed by estimating the population relative risk of the condition in specified groups of relatives.[19] The risk was calculated according to the following equation:

$$\frac{\text{Probability (relative is affected}|\text{proband is affected)}}{\text{Probability (random member of the population is affected)}}$$

A family aggregation is implied when this risk ratio significantly exceeds 1.

As the prevalence of the conditions depends on sex and age (table I) the value of the denominator was adjusted according to the distribution of sex and age in the group of relatives studied.[15] Hence, this standardised population relative risk was estimated by dividing the observed number of affected first degree relatives by the expected number according to the prevalence rates in the population. The expected number was calculated by adding the products of the current sex and age specific rates and the number of relatives within each corresponding sex-age category. The adjusted population relative risk of the two types of migraine were estimated separately. The χ^2 test was used. A 5% level of significance was used. The 95% confidence intervals of the prevalence ratios and the population relative risk were estimated according to the assumption that the numbers affected followed a binomial distribution.

Results

Adequate information was obtained from 378 of the 410 probands. Table II shows the family history.

Table III shows the prevalences of migraine with and without aura among the first degree relatives. As the prevalence of the conditions depends on sex and age (table I) a sex and age standardised population relative risk was estimated for first degree relatives (table IV). The population relative risk of migraine without aura was 1·9 in first degree relatives of probands with migraine without aura. The risk of migraine with aura in first degree relatives of probands with migraine with aura was 3·8. The risks of migraine with and without aura were 2·2 and 1·6, respectively, in first degree relatives of probands with both types of migraine, whereas first degree relatives of probands who had never had migraine had no increased risk of either type.

Tables V and VI show the effect of selected variables on the population relative risk of migraine with and without aura among first degree relatives of probands with and without aura. The population relative risk was not influenced by generation, sex of the probands, age of probands at onset, or by the age of the first degree relatives. The population relative risk tended to increase, however, with descending generation of probands with migraine without aura.

The 106 spouses of probands with migraine without aura had a significantly increased risk of migraine without aura (table IV). The mean (SD) age at onset of migraine without aura was not significantly different among probands (17 (8·0) years) and their spouses (18·6 (10·4)). The 92 spouses of probands with migraine with aura had no increase in the risk of migraine with aura (table IV). There were 15 spouses of probands with both types of migraine; four had migraine without aura. There were 16 spouses of probands who had never had migraine; one had migraine without aura.

Discussion

Our study was based on a relatively large group of thoroughly characterised probands from the general population. An epidemiological study conducted in the same area has yielded reliable prevalence rates for the

general population.[14 15 20] Thus it was possible to calculate the sex and age standardised population relative risk among the first degree relatives and spouses of our probands. All interviews were done by one interviewer as multiple interviewers invariably increase diagnostic variability.[21] Diagnosis of migraine is difficult, and only interviews by physicians with experience in diagnosis of headache can be considered as valid in genetic epidemiological studies of migraine.[14 15 22] Migraine is a subjective complaint, which was the reason interviews of spouses and first degree relatives were blinded to avoid interviewer bias. The present study met the highest possible standards for a genetic epidemiological study of migraine in several other ways. A more detailed discussion of the epidemiological data has been published elsewhere.[15] Migraine without aura and migraine with aura were analysed separately because of clinical and pathophysiological differences.[15 20 23 24] Finally, the quite different familial patterns indicate that the two types of migraine have different causes.

The results concerning migraine without aura were slightly surprising. The risk of migraine without aura among first degree relatives of probands with migraine

without aura was increased only by a factor of two compared with the risk in the general population (population relative risk) or compared with the risk among first degree relatives of probands who had never had migraine. The risk of migraine without aura among spouses was increased by a factor of 1·5. This cannot be explained by assortative mating as migraineurs do not have specific personalities, marital status, education, or employment.[25] Nor can it be explained by environmental factors alone as age at onset of migraine without aura was almost the same in probands and spouses. Presumably a combination of shared environment and simple chance may explain the effect we observed. The increased risk of migraine without aura among spouses may explain the trend toward an increased population relative risk among children of probands with migraine without aura (table V). The results indicate that both genetic and environmental factors may have a relatively weak influence on migraine without aura.

The pattern in migraine with aura was quite different. The risk among first degree relatives of probands with migraine with aura was increased by a factor of 3·8 as compared with the general population or by a factor of six as compared with the risk among first degree relatives of probands who had never had migraine. Spouses of probands with migraine with aura had no increased risk of migraine with aura. The results suggest that genetic factors are of considerable importance. In this context it should be pointed out that because of the high prevalence of migraine with aura (7%) the maximum increase in the population relative risk (when all first degree relatives are affected) is 15.

In summary our results indicate that migraine with and without aura have a different aetiology. The moderate but significantly increased risk of migraine without aura among first degree relatives of probands with migraine without aura is most likely due to a combination of both genetic and environmental factors, whereas the much more increased risk of migraine with aura among first degree relatives of probands with migraine with aura seems to depend primarily or exclusively on genetic factors.

TABLE V—*Effect of selected variables on population relative risk of migraine without aura among first degree relatives of probands with migraine without aura*

Variable	Total No of first degree relatives	No of affected first degree relatives		Population relative risk* (estimated 95% confidence interval)
		Observed	Expected	
Generation:				
Parents	151	40	25·52	1·56 (1·16 to 1·97)
Siblings	167	51	26·12	1·95 (1·51 to 2·40)
Children	36	11	3·21	3·43 (1·65 to 5·21)
Sex of proband/relative:				
Male/male	110	15	10·40	1·44 (0·76 to 2·12)
Male/female	102	38	21·48	1·77 (1·32 to 2·21)
Female/male	61	18	5·83	3·09 (1·89 to 4·29)
Female/female	81	31	17·11	1·81 (1·31 to 2·31)
Age (years) of probands at onset:				
0-9	60	16	9·08	1·76 (1·04 to 2·48)
10-19	173	54	26·65	2·03 (1·63 to 2·41)
20-29	96	24	14·96	1·60 (1·05 to 2·16)
30-39	25	8	4·15	1·93 (0·76 to 3·09)
Age (years) of relative at survey:				
18-19	24	6	1·79	3·35 (0·76 to 5·94)
20-29	20	7	2·56	2·73 (1·26 to 4·21)
30-39	70	17	10·40	1·63 (0·96 to 2·30)
40-49	70	24	11·66	2·05 (1·39 to 2·73)
50-59	23	11	3·77	2·92 (0·00 to 6·47)
60-69	99	27	17·12	1·58 (1·06 to 2·09)
⩾70	48	10	7·51	1·33 (1·03 to 1·64)

*Observed number of affected relatives divided by expected number.

TABLE VI—*Effect of selected variables on population relative risk of migraine with aura among first degree relatives of probands with migraine with aura*

Variable	Total No of first degree relatives	No of affected first degree relatives		Population relative risk* (estimated 95% confidence interval)
		Observed	Expected	
Generation:				
Parents	143	55	13·13	4·19 (3·60 to 4·78)
Siblings	174	47	14·04	3·35 (2·53 to 4·17)
Children	42	9	2·10	4·29 (1·54 to 7·03)
Sex of proband/relative:				
Male/male	106	34	7·00	4·85 (3·51 to 6·20)
Male/female	107	35	10·60	3·30 (2·40 to 4·20)
Female/male	68	13	4·22	3·08 (1·57 to 4·58)
Female/female	78	29	7·46	3·89 (2·77 to 5·01)
Age (years) of probands at onset:				
0-9	53	13	4·04	3·22 (1·70 to 4·73)
10-19	153	56	12·71	4·41 (3·49 to 5·33)
20-29	73	18	6·02	2·99 (1·78 to 4·20)
30-39	80	24	6·47	3·71 (2·48 to 4·93)
Age (years) of relative at survey:				
18-19	24	5	1·06	4·72 (1·02 to 8·41)
20-29	26	7	1·48	4·73 (1·77 to 7·69)
30-39	67	14	5·21	2·68 (1·45 to 3·93)
40-49	78	25	6·68	3·74 (2·54 to 4·94)
50-59	21	5	1·71	2·92 (0·60 to 5·25)
60-69	93	39	8·68	4·61 (3·36 to 5·63)
⩾70	50	16	4·45	3·60 (2·14 to 5·05)

*Observed number of affected relatives divided by expected number.

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Exercise responses and psychiatric disorder in chronic fatigue syndrome

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BMJ 1995;311:544-5

Fatigue, exercise intolerance, and myalgia are cardinal symptoms of the chronic fatigue syndrome, but whether they reflect neuromuscular dysfunction or are a manifestation of depression or other psychiatric or psychological disorders diagnosed in a high proportion of fatigued patients in the community is unclear.[1] In previous studies patients with the chronic fatigue syndrome showed exercise intolerance in incremental exercise tests, which seemed to be related to an increased perception of effort; also, blood lactate concentrations in some patients tended to increase more rapidly than normal at low work rates, implying inefficient aerobic muscle metabolism.[2] We examined venous blood lactate responses to exercise at a work rate below the anaerobic threshold in relation to psychiatric disorder.

Patients, methods, and results

We studied 96 consecutive patients meeting the Oxford criteria for diagnosis of the chronic fatigue syndrome[3] by using the subanaerobic threshold exercise test.[4] Subjects pedalled an electronically braked bicycle ergometer for 15 minutes at 90% of the predicted work rate at their anaerobic threshold, based on age, weight, and sex; venous blood lactate concentrations were measured before, immediately after, and 30 minutes after exercise. Continuous electrocardiographic monitoring allowed measurement of mean heart rate during exercise. An abnormal result was defined as lactate concentrations exceeding the upper 99% reference limit for normal control subjects[4] at two or more time points. We screened a convenience sample of 43 of the 96 patients using 11 established neuropsychological and psychiatric instruments, including the present state examination, for assessment of psychiatric caseness and prediction of psychiatric diagnoses.[5]

The study group comprised 41 men and 55 women of similar age range. Duration of symptoms ranged from six months to 20 years (mean 43·5 (SD 11·6) months). All patients were ambulant.

Thirty one (12 men, 19 women) of the 96 patients (32%) had abnormal lactate responses to exercise (subanaerobic threshold exercise test positive). These patients did not differ significantly from those with normal lactate responses in age, sex, or duration of symptoms. Twenty nine patients (30%) had mean heart rates above the predicted upper 95% reference limit for normal controls.[4] However, there was no significant difference between the proportions with abnormal heart rates among those with abnormal and normal lactate responses (7/31 v 22/63 (no data in two cases); odds ratio 0·54 (95% confidence interval 0·2 to 1·46)).

The 43 patients studied by psychological and psychiatric tests did not differ significantly from the 53 other patients in terms of age (mean 34·6 v 34·4 years); mean duration of symptoms (43·6 v 37·1 months); sex distribution (19 men v 24 men); whether they were working (27 unemployed v 27 unemployed (not recorded in two cases)); or proportion with abnormal lactate responses (15/43 v 16/53). Eighteen of the 43 (42%) patients fulfilled criteria for psychiatric caseness. Diagnoses were neurotic depression (12 patients), manic depression (3), phobic anxiety (2), and anxiety state (1). Patients with normal lactate responses were more likely to fulfil criteria for psychiatric caseness than those with abnormal lactate responses (15/28 v 3/15; odds ratio 4·6 (1·06 to 20·1)).

Comment

Patients with symptoms that precluded or severely restricted physical activity might be expected to show increased lactate responses to exercise as a result of "deconditioning." However, abnormal lactate responses were seen in only a third of our cases, and we found no relation between lactate responses and duration of symptoms or any other demographic variable. Furthermore, although 30% of all patients had abnormally high heart rates during exercise, a high heart rate was as common in patients with normal lactate responses as it was in those with abnormal responses. Patients with the chronic fatigue syndrome who also had psychiatric disorders such as depression, which is commonly associated with fatigue and inactivity, might also be expected to be unfit and to have abnormal exercise results; but the converse proved to be true.

Our results suggest that some patients with the chronic fatigue syndrome have impaired muscle