SHORT REPORT

Genetic loading in familial migraine with aura

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Migraine with aura (MA) arises from a combination of genetic and environmental factors. The sibling risk, age at onset, and aura type were compared in 54 MA probands categorised by family history of MA. Three family types were ascertained each having an MA proband and: (1) an MA parent and MA offspring (three generation; $n=15$), (2) either an MA parent or an MA offspring (two generation; $n=20$), and (3) neither an MA parent nor an MA offspring (one generation; $n=19$). The crude recurrence risk to siblings of probands was 2.7-fold higher in three generation compared with two generation MA families ($\chi^2=6.24$, $p=0.0125$) and 4.8-fold higher in three generation compared with one generation MA families ($\chi^2=9.95$, $p<0.002$). The mean age at onset decreased with an increase in genetic load. The MA probands from three generation families were significantly younger than probands from the one generation families ($F=5.14$, $p=0.030$). MA probands from three generation families were more likely to report more than one type of aura than MA probands from two generation families ($\chi^2=4.44$, $p=0.035$). The significant difference in genetic loading and the earlier age at onset in the three generation families add further evidence for a genetic basis for MA and the difference in sibling risks demonstrates that the MA population is heterogeneous.

Migraine with aura (MA) is a common neurological disorder in the general population with a lifetime population prevalence of less than 10%.¹ Population based segregation analyses,² family,³ and twin studies⁴ support an underlying genetic susceptibility to MA and this susceptibility is generally recognised as arising from a combination of genetic and environmental factors.^{2,4} In the general population, there is a broad range of MA family types with varying degrees of family history or genetic loading. Given that MA probably segregates as a complex trait with incomplete penetrance, phenocopies, and locus heterogeneity, strategies to reduce the genetic heterogeneity within a sample will be of importance in identifying the MA susceptibility genes.

The aim of this study is to develop a rationale for selecting MA families for genetic studies. We have therefore examined the sibling risk, age at onset, and complexity of the aura between 54 three generation Canadian families stratified by the number of generations of vertical transmission of MA.

METHODS

Selection and headache classification of study participants

The probands (63 male, 167 female) for this study were coded as MA from clinic records (GPAP 1994–1998, JDB 1991–1998). These patients with MA were first examined by their family physician who then decided whether to refer based on clinical presentation. Study participants were interviewed by telephone using a semi-structured headache questionnaire that identified headache pain characteristics, the frequency and

Figure 1 Minimum inclusion criteria for MA families: (A) one generation families with only an MA proband, (B) two generation MA families with an MA parent or an MA offspring, and (C) three generation MA families with both an MA parent and at least one MA offspring. Note that siblings of the proband are not a criteria for categorising the families and are therefore not included in the pedigree drawings. Circles, females; squares, males; diamonds, sex not specified; filled in circles and squares, MA; arrow, proband.

age of onset of the headaches, the presence of accompanying autonomic disturbances, and type of aura symptoms.^{3,6} Parents, siblings, and offspring of the MA probands were interviewed using the same questionnaire regardless of whether they reported having headaches. Participants were classified as MA, MO, MA and MO or no migraine based on the International Headache Society (IHS) classification for migraine.⁷ Interviews were conducted by a qualified neurologist who was blinded to the stratification strategy. The catchment area for study participants and their families included London, Canada and surrounding communities. Written consent was obtained from all study participants.

Categorisation of families based on family history of MA

Two hundred and thirty subjects were coded with a diagnosis of MA. After review of the clinic records and an initial telephone call, 108 probands (47.0%) agreed to participate in the study, 84 probands (36.5%) were determined to be non-participants because they declined participation ($n=39$) or could not be located ($n=45$), and 38 probands (16.5%) were determined to have MA caused by associated disorders and were therefore excluded. Of the 108 participating probands, 54 probands (50.0%) were eligible for the study as the migraine status of the proband's parents, spouse, siblings, and offspring could be ascertained. A total of 392 first degree relatives were interviewed. The 54 remaining interviewed probands were ineligible for the study as 45 (41.7%) probands did not have any offspring and could not be classified as a two generation or three generation MA family and nine (8.3%) probands were a conjugal MA/MA or MA/MO mating pair. Probands and family members with MA could also have a co-occurrence of MO.

The 54 MA probands were categorised by family history of MA as follows: (1) an affected parent and at least one affected offspring (three generation; $n=15$; 27.8%), (2) an affected parent or at least one affected offspring (two generation; $n=20$, 37.0%), and (3) neither an affected parent nor an affected offspring (one generation; $n=19$, 35.2%). For this stratification scheme, the proband was always in the second generation and as importantly, affected siblings were not a criteria for inclusion (fig 1).

Table 1 Statistical comparison of risk to siblings of probands, and age at onset and aura type of probands stratified by family history of migraine with aura

(A) Risk to siblings (MA siblings (n)/total siblings (n))	Two generation	Three generation
one generation (3/39; 7.8%)	NS	$\chi^2=9.95$, $p<0.002$
two generations (7/51; 13.7%)	†	$\chi^2=6.24$, $p=0.0125$
three generations (19/51; 37.3%)	†	†
(B) Mean (SD) age at onset (AO) of MA probands	Two generation	Three generation
one generation (26.1 (11.7))	NS	$F=5.138$, $p=0.030$
two generation (21.7 (8.7))	†	NS
three generation (17.6 (8.1))	†	†
(C) Aura type of MA probands (probands with visual aura (n) plus*/ total probands (n))	Two generation	Three generation
one generation (13/19; 68.4%)	NS	NS
two generation (11/20; 55.0%)	†	$\chi^2=4.44$, $p=0.035$
three generation (14/15; 93.3%)	†	†

*Visual aura plus refers to proband report of visual plus one of aphasic, sensory or motor aura; NS, not significant; †no comparison performed; SD, standard deviation.

Statistical analyses

The crude recurrence risk was calculated as the number of siblings with MA/total number of siblings. A χ^2 analysis was performed to test for the significance of the comparison of the proportions. The comparisons of mean age were performed using single factor analysis of variance.

RESULTS

MA probands

There is no difference in the sex distribution ($\chi^2=0.076$, $p=0.78$) or mean (SD) current age ($F=2.28$, $p=0.13$) of the 108 participating MA probands (41.3 (11.6) years) and the 84 non-participants (44.2 (13.1) years). The female to male gender ratios were 3.0:1.0 for the participants and 2.5:1.0 for the non-participants.

The 54 MA probands were referred for: changes to the complexity of their aura ($n=15$; 27.8%), required more efficacious medication ($n=16$; 29.6%), reactivation of dormant MA at menopause ($n=5$; 9.3%), occurrence of aura alone after years of MA episodes ($n=2$; 3.7%), increased frequency of MA ($n=6$; 11.1%), or MA identified as part of history taking for another headache type or other neurological disorder ($n=10$; 18.5%).

Genetic load and risk to siblings

The 54 MA probands had a total of 154 siblings. One hundred and forty one of the siblings were interviewed and 29 (20.1%) had MA by IHS criteria.⁷ The remaining 112 unaffected siblings were all older than 30 years of age and 82% ($n=92$) were older than 40 years of age. Fifty three (98.1%) of the MA probands were greater than 30 years of age and 70.4% ($n=38$) were greater than 40 years of age. There was no difference in the mean current age of the MA probands and the unaffected siblings (45.7 (10.4) years versus 47.2 (12.5) years; $F=0.62$, $p=0.433$).

The risk to siblings increased with an increasing genetic load of MA. The crude recurrence risk to siblings of three generation MA families was 37.3% (19 of 51) and was significantly greater than siblings from one generation families at 7.8% (3 of 39) ($\chi^2=9.95$, $p<0.002$) and also significantly greater than sibling risk in two generation MA families at 13.7% (7 of 51) ($\chi^2=6.24$, $p=0.0125$) (table 1A). A group comparison of all three sibling risks was significant ($\chi^2=15.004$, $p<0.005$).

Age at onset and genetic load

The MA probands from three generation MA families (17.6 (8.1)) were significantly younger than MA probands from the one generation (26.1 (11.7)) ($F=5.138$, $p=0.030$), but not the

two generation MA families (21.7 (8.7)) ($F=1.923$, $p=0.174$) (table 1B). There is a significant difference in age at onset of MA between all three groups ($F=3.204$, $p=0.049$).

Aura and genetic load

The severity of MA, as measured by type of aura, was assessed in the 54 MA probands. Participants were categorised as having visual aura only or as having visual aura plus at least one other type of aura (aphasic, sensory, or motor) for a minimum of one aura episode (table 1C). The probands from the three generation MA families (14 of 15; 93.3%) reported a broader range of aura type than either the two generation (11 of 20; 55.0%) or one generation (13 of 19; 68.4%) MA families and MA probands with both an MA parent and an MA child were significantly more likely to exhibit visual plus other aura types than MA probands with either an MA parent or an MA child only ($\chi^2=4.44$, $p=0.035$). The range of aura type was comparable for the one generation and two generation MA families ($\chi^2=0.283$, $p=0.595$).

DISCUSSION

The siblings of MA probands have a significantly 2.7-fold higher crude recurrence risk to siblings in three generation than in the two generation MA families and a significantly higher 4.8-fold risk in three generation than in one generation families. The risk to siblings in the one generation MA families, a family type that corresponds to phenotypically sporadic MA cases in the general population, is similar to a reported population prevalence of MA.¹ In contrast, two generation and three generation families have substantially higher risks to siblings compared with the general population.

Age at onset was also examined as a measure of the severity of MA as a younger age at onset of disease is a hallmark of the familial form of many disorders in the general population such as early onset breast cancer⁸ and early onset Alzheimer's disease.⁹ Sibling risk increases with a decreasing age at onset of the proband for multiple sclerosis¹⁰ and breast cancer.¹¹ More significantly, stratification of relatively prevalent disorders by age at onset made it possible to identify linkage in multiplex families with apparent autosomal dominant mode of inheritance^{12,13} and ultimately, to identify the causative genes (BRCA1,¹⁴ pre-senilin-1¹⁵). In our data, there is an observable downward trend in mean age at onset of the proband that corresponds with an increasing degree of genetic loading. The probands from three generation MA families were significantly younger than the MA probands from the one generation MA families. Age at onset should therefore be an additional consideration for selecting MA families for genetic studies.

As almost all people with MA have visual aura,¹⁶ we used the presence of non-visual types of aura as a measure of severity of MA. Ninety three per cent of probands from three generation MA families reported a broader range of aura type than probands from two generation (55.0%) and one generation (68.4%) MA families. The broader range of aura described by the probands of the three generation MA families is consistent with the greater genetic load that corresponds to a higher risk to siblings and the lower age at onset in this type of family. In a Finnish clinic population of MA or MA and MO probands with family history of migraine, a broader range of aura types was also reported for at least 50% of the probands.¹⁷

In this study, we identified 192 MA probands from coded patient records and interviewed 108 probands and available first degree relatives. The referral practices of family physicians and the modest participation rate (56.3%) of the identified MA probands in this study are potential sources for selection bias. We found no difference in the sex ratio or mean current age of the 108 participants and the 84 non-participants. We also determined that all 54 MA probands sought specialised care because of medical needs, as adults (39.2 (10.9) years) about 17 years after their initial episode and independent of family history. Thus, these potential sources of bias should not affect the observed degree of genetic loading in our MA families. Clinic based MA probands may differ to probands in the general population as a high percentage of the 54 probands (70.4%) reported a more complex aura than was found for probands in a population based study.¹⁶ However, in this study we are comparing sibling risk, age at onset, and complexity of the aura between three groups likely to be biased in the same way. Although we believe that the lower age at onset and increased sibling risk in MA families when MA is vertically transmitted through three generations is probably applicable to MA in the general population, these results need to be confirmed in a population based cohort.

MA arises from a combination of genetic and environmental factors and it has been suggested that MA be considered a complex trait for genetic studies. The spectrum of MA family types, ranging from phenotypically sporadic MA through varying degrees of family history, contributes to an overall complex picture for the genetic susceptibility to MA, but the complexity can be reduced by stratifying MA families by family history. For example, the proportion of MA siblings in our three generation MA families is consistent with an autosomal dominant mode of inheritance with reduced penetrance. Parametric linkage analysis of such enriched multiplex families may be a rewarding strategy as demonstrated by the identification of the early onset breast cancer¹² and early onset Alzheimer's disease¹³ susceptibility genes. The significant linkage of MA to 4q24¹⁸ supports the utility of parametric linkage analysis of large, multiplex families enriched for MA. By selecting for MA families with a high penetrance of MA and age at onset in the mid-teenage to late teenage years, we should be selecting for families with a greater genetic load and fewer confounding factors attributable to environmental effects and ultimately, a more homogenous MA cohort.

The stratification of three generation families into those with one, two, or three generations of family history of MA has allowed us to evaluate MA with respect to genetic loading and risk to siblings, age at onset, and type of aura. The significant difference in genetic loading and earlier age at onset in the three generation MA families adds further evidence for a

genetic basis for MA and the heterogeneity illustrated by the increased sibling risk in subtypes of MA probands emphasises the complexity of MA in the general population.

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