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Accuracy of Family History Reports of Migraine in a Community-Based Family Study of Migraine

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Abstract

Objective—The aim of the present study was to assess the validity of migraine diagnosis provided by family history compared to direct interview using a validated diagnostic interview of headache syndromes in the context of a family study of migraine comorbidity.

Background—Family history of migraine is the most potent and consistent risk factor for migraine. However, there has been limited systematic research on the reliability of family history information in detecting migraine based on valid diagnostic interviews. This study systematically evaluated the accuracy of migraine defined by the International Classification of Headache Disorders (ICHD-II) based on a direct structured interview compared to structured family history reports.

Methods—The sample included 921 study participants identified in a cross-sectional community based controlled family study of comorbidity of migraine and affective disorders recruited from the greater Washington, D.C. community. Lifetime migraine and tension-type headache were ascertained by direct clinical interview using a validated interview that collects ICHD-II criteria for headache syndromes. A structured history of headache was also collected from all interviewed probands and relatives regarding their relatives. All family history reports were reviewed by the study neurologist according to ICHD-II criteria. Family history ratings and diagnoses were made by the neurologist who was blinded to the headache diagnosis obtained by direct interview.

Results—The sensitivity and specificity of family history reports of migraine compared to direct interview were 38.6% and 96.8%, respectively, indicating that the false positive rate was very low, whereas the false negative rate was substantial. The positive and negative predictive values of migraine diagnosis provided by family member report are 90.0% and 67.6% respectively.

Conclusions—Our results confirm that migraine assessed by family member report largely underestimates migraine in relatives. This demonstrates the value of direct interviews with relatives rather than reliance on family history report in both clinical practice and family and

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genetic studies. Potential steps to improve the reliability of family history report in clinical settings are described.

Keywords

migraine; family studies; family history

BACKGROUND

The diagnosis of migraine headaches is determined entirely by clinical history based on a constellation of symptoms and exclusion of an alternative etiology[1]. A family history of migraine is the most potent and consistent risk factor for migraine, with a two-to-three-fold greater risk of migraine among relatives of people with migraine compared to controls[3–5]. Migraineurs with a positive family history tend to have an earlier onset of headache symtoms and greater severity[6] than those without a family history. Moreover, patients with transformed migraine also have a significantly greater prevalence of a positive family history of migraine than those without[7]. Family history of disorders is important for clinical evaluation and treatment decisions as well as for identifying genetic factors underlying migraine. In fact, a positive family history was included as a diagnostic criterion in the ad hoc diagnostic criteria for migraine[2].

Due to the lack of pathognomonic biologic markers for migraine, the diagnosis is determined entirely by clinical history based on a constellation of symptoms and exclusion of an alternative etiology[1]. Therefore, most family studies[8–10] have relied on family history reports regarding symptoms and signs of migraine obtained from the patients with migraine rather than on direct interviews of the relatives. Only one family study[11] utilizing International Headache Society (IHS) criteria, performed almost 2 decades ago, that systematically evaluated the validity of migraine assessed by proband report found that there was significant underestimation of migraine in relatives. Likewise, Ottman et al[15] reported a high false negative rate (and low sensitivity) in informant reports regarding migraine in relatives. By contrast, they found greater accuracy for family history information regarding epilepsy in relatives, perhaps attributable to the more observable nature of seizures[12].

In contrast to the dearth of studies of family history report of migraine, the field of psychiatry has devoted substantial effort to research on factors associated with reliability of family history reports. A meta-analysis of the existing studies on validity, reliability and objectivity of the family history for various psychiatric diseases found wide variability in the validity of family history across the different disorders with family history reports of schizophrenia and substance abuse being much more valid than depression and anxiety. Significant effects were observed with age but not with sex of the informant for all these psychiatric disorders[13].

In the present study, our aim was to assess the accuracy of migraine diagnosis provided by family members about their directly interviewed relatives using a validated diagnostic interview of relatives as the gold standard.

METHODS

Sample

The study sample consisted of 921 adults (556 female, 365 males), ages 18 through 96 years, identified within a large community family study of comorbidity of migraine and affective disorders conducted at the Clinical Center of the National Institute of Mental Health (NIMH)[17]. The probands were recruited from a community screening of the greater Washington, D.C. metropolitan area with clinical enrichment from individuals who were screened in the NIMH Mood and Anxiety Disorder Program the National Institutes of Health (NIH) from June 2004 through June 2012. The community sample was recruited through screening of a sample of 11,000 households, within 50 miles of Washington, D.C. obtained from a marketing survey list. This sampling strategy was not intended to obtain a representative sample of the greater Washington area, but rather to obtain a non-clinical sample to reduce the bias inherent in those recruited from specialty settings. Inclusion criteria were an ability to speak English, and availability of and consent to contact at least two living first degree relatives. Telephone interviews were conducted with those who could not visit the NIH.

Standard family study methodology was employed including direct interviews of probands and relatives by experienced clinicians, systematic enumeration of relatives including children, blind assessment of relatives, and structured family history interviews regarding all probands and relatives[18]. The study was approved by the Combined Neuroscience IRB at the NIH, and all subjects provided written informed consent.

Family history information was systematically collected from probands and all interviewed relatives regarding living and deceased adult relatives including the proband. There was an average of one adult sibling and offspring per proband. From this larger family study we identified 921 subjects (including probands and relatives) with direct structured interviews regarding a history of headache, who had at least one family member report regarding the subject's history of headaches and specific symptoms.

Measures and Validation Procedures

All interviewed probands and relatives were administered the NIH Diagnostic Interview of Headache Syndromes (DIHS) (see Lateef et al[19] for validation of the DIHS in children). This interview was administered by trained study personnel and was used to assess ICHD-II criteria for migraine.

The structured family history for mental disorders, was expanded to assess physical conditions including migraine, sleep disorders and other conditions. The migraine questions were a subset of symptoms from the direct interview that queried a history of headaches, associated symptoms, severity, functional impairment and treatment. According the standard practice in family history method in psychiatry, a diagnosis of migraine was coded positive if any of the relatives reported the presence of migraine in an index case. A final diagnosis of migraine or tension-type headache was made by a neurologist's review of the headache history questionnaires administered to the first degree relatives regarding a particular participant. The study neurologist had experience in the diagnosis and treatment of migraine

and other headaches and was blinded to the headache diagnosis derived from direct clinical interview of the study participants.

Unlike the typical family study design wherein only the proband is asked about relatives, this study also included relative reports on the proband due to fact that the larger family study focus included mental health disorders.

Data Analysis

Concordance between family history reports and direct interviews was estimated by Cohen's kappa[14], sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Diagnosis based on direct interview was used as the gold standard when estimating the sensitivity and specificity. Sensitivity assesses the proportion of actual headache positive subjects (with a diagnosis of headache from the interview) who are correctly identified by the family history reports, while specificity assesses the proportion of those without headache who are correctly classified by the family history. PPV is the proportion of the positive headache diagnoses based on the family history that is confirmed by the interview while NPV states the proportion of the non-headache diagnoses based on the family history that match the diagnoses from the interview. Kappa[14] was used to test whether the agreement between the family history and the interview exceeds chance level. Analyses were conducted using SAS (Copyright (c) 2002–2010 by SAS Institute Inc., Cary, NC, USA).

RESULTS

Of the 921 participants, 396 had migraine with or without aura, 69 had tension type headache, 82 had non-migraine and non-tension type headache and 374 had no history of headaches. Agreement between the headache diagnoses derived from family member report and those from direct interview is shown in Table 1. There were 153 people with migraine based on family member report whereas there were 396 participants who met criteria for migraine on direct interview. Ten participants reported to have tension-type headache and 94 participants who were reported to have other headache types were found to have migraine upon direct interview.

The concordance statistics for family history compared to direct interview are shown in Table 2. The sensitivity and specificity of detecting migraine using family history report are 38.6% (true positives) and 96.8% (true negatives), respectively. The positive and negative predictive values of migraine diagnosis provided by family member report are 90.0% and 67.6% respectively. Thus a large proportion (>60%) of migraineurs would be left undiagnosed on the basis of family member report alone.

Family member report was even less reliable for the diagnosis of tension-type headache, with sensitivity of 6.1% and a specificity of 96.5%. The positive predictive value and negative predictive value of family history compared to direct interview were 29.7% and 80.8%, respectively. The specificity and negative predictive value of parent reports of migraine were 100% and sensitivity remained 37.7%.

DISCUSSION

These findings show that family history reports of migraine yield dramatic under-estimation of the true presence of migraine and tension type headache; relatives accurately report only about 4 out of every 10 cases of migraine and 6 out of every 100 cases of tension-type headache. By contrast, detection of true negatives by relatives was quite accurate.

Our findings confirm those of the two prior studies of family history of migraine that demonstrated under-reporting of migraine in relatives[8,9]. For example, Ottman et al reported sensitivity of 48% for severe headache and 44% for migraine[15], and Russell and colleagues[11] found a sensitivity of 49% by proband report. Whereas the latter study did collect full symptomatic information on relatives, the former study limited inquiry to the presence or absence of a history of migraine or severe headaches. Our somewhat lower sensitivity (i.e., 39%) could have been attributable to the broader nature of our study that was not solely focused on migraine. In neurologic conditions, such as epilepsy, where the manifestations of the disorder can be more obvious, family history reports have been shown to be more reliable (62% sensitivity for all relatives with parent and sibling reports being considerably higher – 90% and 80% respectively)[11].

The lack of reliability of family history reports of migraine should therefore be considered in both clinical and research settings. In family and genetic studies in which misclassification is a serious threat to the validity of the research, effort should be devoted to collect both a systematic pedigree of the number of relatives, and information from multiple family members regarding the objective manifestations of migraine when it is not possible to conduct a direct interview. Psychiatry literature, in particular, suggests that females are better informants, and that information should be weighted to incorporate extent to which the informant lived with or had close knowledge of the relative's symptoms during attacks.

Our family history measure has incorporated the following steps to minimize misclassification of relatives and maximize value of family history:

1. systematic collection of the denominators in order to determine proportions of affected relatives rather than a dichotomous classification of positive or negative history;
2. collection of information on the extent of contact with the index person to discriminate between awareness of migraine symptoms and their consequences; and
3. inclusion of questions that focus on objective manifestations of migraine and the index person's steps to relieve the symptoms and pain.

Since collection of a full pedigree and detailed information on headaches in family members is not feasible in clinical settings, clinicians should at least attempt to obtain an estimate of the number of siblings and offspring and proportions affected in order to obtain a denominator of relatives, as well as inquire regarding most objective characteristics of migraine attacks. Moreover, future studies should attempt to obtain corroboration of negative cases when false negative rates are associated with threats to study validity.

Strengths of this study are the community-based sample, the large number of participants who were thoroughly studied as part of a larger family study of migraine and affective disorders, and the use of structured diagnostic interviews that collect ICHD-II criteria for both the direct interviews and family history interviews. Limitations include the lack of sufficient criterial symptoms on family history report to assess the major subtypes of migraine. Also, we did not assess the full spectrum of headache subtypes, including migraine with and without aura by family history because of the difficulty in obtaining symptoms of aura without direct interview. Finally, these analyses refer only to adult probands and relatives; however, however, our earlier work revealed that parent reports also yield substantial underestimation of migraine[16].

CONCLUSIONS

Our results confirm that migraine assessed by family member report largely underestimates migraine in relatives. This demonstrates the value of direct interviews with relatives rather than reliance on family history report in both clinical practice and family and genetic studies. Steps to improve the reliability of family history report in clinical settings are described.

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Table 1

Agreement on headache diagnoses between family member report and direct clinical interview (n, column %)

FAMILY HISTORY REPORT	DIRECT INTERVIEW				
	Migraine	**Tension-type HA**	**Other HA**	**No HA**	**TOTAL**
Migraine	153 (38.6)	5 (7.3)	10 (12.2)	2 (0.5)	**170**
Tension-type HA	10 (2.5)	0 (0.0)	1 (1.2)	0 (0.0)	**11**
Other HA	94 (23.7)	21 (30.4)	13 (15.9)	53 (14.2)	**181**
No HA	139 (35.1)	43 (62.3)	58 (70.7)	319 (85.3)	**559**
TOTAL	**396**	**69**	**82**	**374**	**921**

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Table 2

Validity of family member report on headache diagnosis (interview as gold standard)

	Any Headache	Migraine	Tension-type
Sensitivity (95% CI)	56.2 (53.0 – 59.4)	38.6 (35.5 – 41.7)	6.1 (4.6 – 7.6)
Specificity (95% CI)	85.1 (82.8 – 87.4)	96.8 (95.7 – 97.9)	96.5 (95.3 – 97.7)
Kappa (95% CI)	0.38 (0.32 – 0.43)	0.38 (0.33 – 0.43)	0.04 (−0.02 – 0.09)
PPV (95% CI)	84.9 (82.6 – 87.2)	90.0 (88.1 – 91.9)	29.7 (26.7 – 32.7)
NPV (95% CI)	57.1 (53.9 – 60.3)	67.6 (64.6 – 70.6)	80.8 (78.3 – 83.3)