Characterization of Familial and Sporadic Migraine

Ravn, Julie; Chalmer, Mona A.; Oehrstroem, Emil L.; Kogelman, Lisette J.A.; Hansen, Thomas F.

Published in:
Headache

DOI:
10.1111/head.13640

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

Headache
© 2019 The Authors. Headache: The Journal of Head and Face Pain
published by Wiley Periodicals, Inc., on behalf of American Headache Society

ISSN 0017-8748
doi: 10.1111/head.13640
Published by Wiley Periodicals, Inc.

Research Submission

Characterization of Familial and Sporadic Migraine

Julie Ravn, MD *; Mona A. Chalmer, MD*; Emil L. Oehrstroem, MD; Lisette J. A. Kogelman, PhD; Thomas F. Hansen, PhD

Background.—It is unknown whether clinical parameters differ between migraineurs with and without first-degree family members with migraine.

Objectives.—The present cross-sectional study describes differences between familial and sporadic migraine with a focus on migraine characteristics, migraine severity, comorbidities, and treatment.

Method.—From the Danish Headache Center we recruited 358 patients with familial migraine and 1727 patients with sporadic migraine. Each participant was assessed using a validated semi-structured interview.

Results.—No differences in age (Mean = 44 and 44 [SD = 12.28 and 12.58] for familial and sporadic migraineurs, respectively; *P* = .900) or sex (295/358 (82.4%) and 1413/1727 (81.8%) women in familial and sporadic migraineurs, respectively; *P* = .853) were found. Familial migraineurs had more aphasic aura than sporadic migraineurs (41% vs 27%, *P* = .001). Sporadic migraineurs had more lifetime attacks ie, >100 attacks (45% vs 70%, *P* < .001) and prolonged attacks ie, lasting >72 hours (5% vs 12%, *P* < .001) than familial migraineurs. Further, sporadic migraineurs had a higher incidence of concussions (37% vs 41%, *P* = .001) compared to familial migraineurs. In agreement with a previous study, there was no difference between familial and sporadic migraine regarding triptan response (84% vs 81%, *P* = .440).

Conclusion.—Headache characteristics, triptan response, and comorbidities where similar in individulas with and without inherited migraine, suggesting that migraine are to be considered a hmogenoues disease. The difference in the clinical presentation of migraine with aura symptoms among patients with familial migraine should be considered in future studies. Further, more severe migraine among patients with sporadic migraine with aura could suggest that sporadic migraineurs have been exposed to stronger or multiple environmental factors and indicate that an early intervention in migraine treatment could lessen the severity of migraine.

Key words: aura, comorbidity, treatment response, clinical characteristics, severity

Abbreviations: ICHD-III International Classification of Headache Disorders 3rd edition, MA migraine with aura, MO migraine without aura, pMA probable migraine with aura, pMO probable migraine with aura

(*Headache* 2019;59:1802-1807)

From the Department of Neurology, Danish Headache Center, Copenhagen University Hospital, Rigshospitalet-Glostrup, Glostrup, Denmark (J. Ravn, M.A. Chalmer, E.L. Oehrstroem, L.J. Kogelman, and T.F. Hansen).

Address all correspondence to T.F. Hansen, Department of Neurology, Danish Headache Center, Copenhagen University Hospital, Rigshospitalet-Glostrup, Glostrup, Denmark, email: thomas.hansen@regionh.dk

Accepted for publication August 12, 2019.

INTRODUCTION

Twin and family studies have shown that migraine is a complex, multifactorial disorder and that there is a considerable genetic component in migraine with an estimated heritability of 38-53%.[1-3] Even though migraine is a highly heritable disorder it also occurs sporadically, that is, in cases where siblings and parents do not have

*Both authors contributed equally.

Conflict of Interest: None

Funding: MAC, LJAK, and TFH are supported by a grant from Candys foundation (CEHEAD). JR has received a student fellowship from the Lundbeck Foundation through the Danish Neurological Society. The funding bodies had no role in the study.

migraine. However, it is unknown whether clinical parameters are different between migraineurs with and without first-degree family members with migraine,[4] ie, familial and sporadic migraine. One study has found an association between a strong family history of migraine and a lower age-at-onset of migraine and higher numbers of medications days,[5] and another study has suggested an association between more severe symptoms and familial aggregation of migraine with aura.[6] We hypothesize that this is true and aim to investigate differences between familial and sporadic migraine with a focus on migraine characteristics, migraine severity, comorbidities, and treatment of both migraines with and without aura. For this cross-sectional study, we use a large cohort of migraineurs (n = 2085) including both familial and sporadic migraine.

MATERIALS AND METHODS

Study Population.—The study population consisted of adult men and women (>18 years of age) recruited via the Danish Headache Centre, Rigshospitalet-Glostrup, Denmark, with migraine with (MA) and without (MO) aura defined by the International Headache Society.[7]

Patients were excluded if they had secondary headache, if they declined, if they had motor aura symptoms (to avoid including patients with one of the known genes of familial hemiplegic aura) or were cognitively not able to complete the semi-structured interview. Probands with reported familial migraine were not included in the study if they did not have at least 1 relative able or willing to participate in a semi-structured interview. Probands were defined as the initial patients recruited from the Danish Headache Centre through convenience sampling. All probands were questioned whether they had any first-degree relatives with migraine and segregated accordingly. The study population was categorized as; (1) sporadic migraine probands (n = 1727); migraine patients from the Danish Headache Centre without migraine in their first-degree relatives; and (2) familial migraine probands, ie, migraine patients from the Danish Headache Centre with at least 1 first-degree relative with migraine (n = 358). Here, 1085 relatives were interviewed and out of these 696 were diagnosed with migraine with or without aura. The median number of relatives with a diagnosis of migraine, was 2 (1st and 3rd quantile respectively 1 and 4).. Family members were not included in this study to avoid ascertainment bias.

The recruitment of familial migraine probands took place between 1999 and 2002 and recruitment of sporadic migraine probands took place during the periods 2005-2006 and 2010-2012 as described elsewhere in 2 preplanned papers.[6,8] Furthermore, a recruitment of familial and sporadic probands following the guideline as previously described continued in the period 2012-2018.

In the first round of recruitment (years 1999-2002) patients with hemiplegic migraine were not included, since nonhemiplegic migraine with aura and familial and sporadic hemiplegic migraine are separate entities in the International Classification of Headache Disorders 2nd Edition.[6]

This study is approved by The National Committee on Health Research Ethics and the Data Protection Agency, file no. H-2-2010-122. Written informed consent was obtained from all participants.

Semi-Structured Interview.—Each subject as well as relatives for familial probands (n = 1085) participated in a revised validated semi-structured interview[9,10] based upon the third edition of the International Classification of Headache Disorders (ICHD-III)[7] performed by a neurologist or a senior medical student specifically trained in headache diagnostics to derive the correct diagnose. The interview was conducted face-to-face or through telephone.

The patients were asked to describe their headache without the use of prophylactic or acute medication and were asked whether the headache was unilateral, had a pulsating character, intensity of the headache, aggravation by routine activity, occurrence of vomiting or nausea, and if they experienced photo- and phonophobia. Furthermore, if they had visual aura, they were asked whether it was unilateral, gradually developing, presence of scotoma, fortification and/or flickering light, nonpreserved central vision and the duration of the gradual development as well as the total duration of the visual aura. Patients with sensory aura were asked if it was unilateral, gradual developing, which areas of the body were affected, as well as the duration of the development and total duration of the sensory aura. For aphasic, aura patients were asked

if they had dysarthria, paraphasia, impaired comprehension or production of speech and the duration of the aphasic aura.

Less than 2% in both groups presented motor aura symptoms and was not further analyzed due to low statistical power and all patients with hemiplegic migraine were excluded (cf. "Study Population" in the method section).

Adapting the definition of migraine severity from Esserlind et al,[11] the severity of migraine was assessed based upon the onset of migraine <10 years of age, >100 lifetime attacks, migraine attacks >72 hours, and chronic migraine.

Triptan response was defined as 50% reduction in pain within 2 hours after intake. Patients were asked if they had somatic comorbidities (concussion, meningitis, epilepsy, stroke, cerebral hemorrhage, high blood pressure, cardiovascular disease, and metabolism disorders) and whether a doctor had given them the diagnosis. Thus, only diagnosis given by a physician was recorded.

All patients diagnosed with MA, probable MA (pMA), MO, and probable MO (pMO) were included in the study. Finally, all questionnaires were obtained using the open source questionnaire tool LimeSurvey©.

Statistical Analysis.—For statistical analysis, patients with pMA and MA were analyzed together and patients with pMO and MO were analyzed together; patients with both MA and MO were analyzed as MA. Statistical analyses were performed using statistical software R version 3.3.2 and R Studio version 1.0.136.

We investigated the characteristics of migraine between familial and sporadic migraine in 39 parameters. Bonferroni's correction for multiple testing was applied, resulting in a significant *P* value threshold of .0013. The 39 parameters are the number of individual tests, as the subdivision into "MA," "MO," and "Combined migraineurs" is considered post-hoc analyses.

No statistical power calculation was conducted prior to the study, as the study is considered a post-hoc based on previously retrieved data. Missing data in a question led to exclusion from the specific analyses.

For the demographical characteristics of the population a two-sided t-test was used for age after checking that data were normally distributed using a graphical approach, and chi-square test was used for sex.

In the analysis, the population was divided into groups by clinical characteristics and compared using logistic regression correcting for sex and age using them as covariates. When comparing the median duration of clinical symptoms, the Wilcoxon rank-sum test was performed as data were not normally distributed.

RESULTS

Demographic Profile.—Comparing patients with familial (n = 358) and sporadic (n = 1727) migraine we found no differences in age (Mean = 44 and 44 [SD = 12.28 and 12.58] for familial and sporadic migraineurs, respectively; $P = .900$) or sex (295/358 (82.4%) and 1413/1727 (81.8%) women in familial and sporadic migraineurs, respectively; $P = .853$).

Aura Characteristics.—In total, there were 73% (263/358) of familial and 44% (760/1727) of sporadic migraineurs fulfilling the diagnostic criteria of MA ($P < .001$).

Visual Aura.—The visual aura, Table 1, was more often gradually developed, unilateral flickering lights for both familial and sporadic migraine. A total of 11 individuals (3 familial and 8 sporadic migraineurs) had incomplete data and were excluded from the analysis of visual aura. The visual aura comprised of a scotoma more often in familial than sporadic migraine ($P < .001$); occurring in 66.4% of familial vs 50.8% of sporadic migraineurs. There was less commonly nonpreserved central vision in familial than sporadic migraineurs; 20.4% vs 33.6% ($P < .001$).

Sensory Aura.—When comparing sensory aura, Table 1, between the groups, no difference was found. A total of 8 individuals (1 familial and 7 sporadic migraineurs) had incomplete data and were excluded from the analysis of sensory aura.

Aphasic Aura.—Familial migraineurs had more often dysphasic aura than sporadic migraineurs ($P < .001$). Moreover, sporadic migraineurs had a significantly higher frequency of impaired comprehension of speech ($P < .001$) compared to familial migraineurs, Table 1. A total of 8 individuals (1 familial and 7 sporadic migraineurs) had incomplete data and were excluded from the analysis of dysphasic aura.

Table 1.—*Aura in Patients With Familial and Sporadic Migraine With Aura*

	Familial (n = 263)	Sporadic (n = 760)	*P* Value
Visual aura, n (% of all MA patients)	248 (94)	717 (94)	.877†
Unilateral, n (% of visual aura patients)	183 (74)	510 (71)	.270†
Gradually developing, n (% of visual aura patients)	197 (79)	562 (78)	.763†
Scotoma, n (% of visual aura patients)	164 (66)	369 (51)	**<.001**†
Zig-zag lines (fortification), n (% of visual aura patients)	118 (48)	316 (44)	.212†
Flickering light, n (% of visual aura patients)	207 (83)	603 (84)	.844†
Nonpreserved central vision, n (% of visual aura patients)	49 (20)	238 (33)	**<.001**†
Duration of gradual development in minutes, median [25th, 75th]	15 [5, 20]	10 [5, 20]	.500‡
Duration of visual aura in minutes, median [25th, 75th]	30 [20, 45]	30 [20, 60]	.008‡
Sensory aura, n (% of all MA)	143 (54)	374 (49)	.243†
Unilateral, n (% of sensory aura patients)	124 (87)	322 (86)	.720†
Gradually developing, n (% of sensory aura patients	103 (72)	238 (64)	.026†
Sensation of sensory aura in the: n (% of sensory aura patients)			
Face	102 (71)	246 (66)	.202†
Tongue	55 (38)	166 (44)	.218†
Hand	126 (88)	284 (76)	.004†
Arm	77 (54)	235 (63)	.039†
Foot	21 (15)	91 (24)	.019†
Leg	23 (16)	79 (21)	.206†
Body	12 (8)	44 (12)	.281
Duration of gradual development in minutes, median [25th, 75th]	15 [6.5, 30]	13 [5, 30]	.305‡
Duration of sensory aura in minutes, median [25th, 75th]	30 [20, 60]	45 [20, 60]	.134‡
Dysphasic aura, n (% of all MA)	109 (41)	204 (27)	**<.001**†
Dysarthria, n (% of aphasic aura patients)	46 (42)	81 (40)	.008†
Paraphasia, n (% of aphasic aura patients)	92 (84)	152 (75)	.058†
Impaired comprehension of speech, n (% of aphasic aura patients)	84 (77)	165 (81)	**<.001**†
Impaired production of speech, n (% of aphasic aura patients)	33 (30)	71 (35)	.005†
Duration of dysphasic aura in minutes, median [25th, 75th]	15 [3, 45]	30 [17, 60]	.390‡

†Logistic regression with covariate age and sex.
‡Wilcoxon rank-sum test.
Significant *P* values after multiple testing are marked in bold.

Migraine Severity.—Sporadic migraineurs had more lifetime attacks ($P < .001$) as well as prolonged migraine attacks ($P < .001$) compared to familial migraineurs suggesting a slightly higher severity profile among sporadic than familial migraine, Table 2. No missing data were found when analyzing migraine severity.

Headache Characteristics.—We did not see any difference in headache characteristics between familial and sporadic migraine (see Supplementary Table S1). No missing data were seen.

Comorbidities.—Sporadic migraineurs without aura had more concussions than familial migraineurs ($P = .001$) (Supplementary Table S2). No other differences between the groups were found, and no missing data were seen.

Triptan Response.—There was no difference in the triptan response rate between familial and sporadic migraineurs, neither when comparing MO patients ($P = .858$), MA patients ($P = .112$) nor when comparing all migraineurs ($P = .440$). (Supplementary Table S3). A total of 421 individuals (180 familial and 241 sporadic migraineurs) had incomplete data and were excluded from the analysis of triptan response.

DISCUSSION

This study is the largest study to date comparing familial to sporadic migraine. The study investigated whether clinical parameters differ between migraineurs with and without first-degree family members with migraine. Familial migraine with aura patients more often had scotoma and aphasic aura than patients with

Table 2.—Migraine Severity in Patients With Familial and Sporadic Migraine

	Familial (n = 358), n (%)†	Sporadic (n = 1727), n (%)‡	*P* Value§
Early onset of migraine (<10 years)			
MO (% of MO)	14 (15)	173 (18)	.555
MA (% of MA)	38 (14)	132 (17)	.228
Combined (%)	52 (15)	305 (18)	.149
Many lifetime attacks (>100 attacks)			
MO (% of MO)	83 (87)	840 (87)	.940
MA (% of MA)	77 (29)	369 (49)	**<.001**
Combined (%)	160 (45)	1209 (70)	<.001
Prolonged migraine attacks (>72 hours)			
MO (% of MO)	9 (10)	132 (14)	.251
MA (% of MA)	9 (3)	78 (10)	**<.001**
Combined (%)	18 (5)	210 (12)	**<.001**
Chronic migraine			
MO (% of MO)	16 (17)	115 (12)	.157
MA (% of MA)	14 (5)	81 (11)	.008
Combined (%)	30 (8)	196 (11)	.100

†Total number is 358, out of these 263 had migraine with aura (MA) and 95 had migraine without aura (MO).
‡The total number is 1727, out of these 760 had migraine with aura (MA) and 967 had migraine without aura (MO).
§Logistic regression covariate with age and sex.
Significant *P* values after multiple testing are marked in bold.
MA = migraine with aura; MO = migraine without aura. Combined = probands regardless of with or without aura.

sporadic migraine. Furthermore, sporadic migraineurs with aura had more often prolonged attacks as well as more lifetime attacks.

There was no difference with regards to triptan response, which is in agreement with a previous study,[4] and likewise when comparing migraine characteristics. Regarding comorbidities, the difference between the groups was sparse, but sporadic migraineurs without aura had a higher incidence of concussion.

In this study, 94% of migraineurs with aura experienced visual aura symptoms regardless of being sporadic or familial migraineurs. The higher incidence of preserved central vision and scotoma in familial migraineurs is in agreement with a previous study conducted in a smaller part of the same cohort.[6]

Unexspected, given our original hypothesis, sporadic migraineurs with aura had more severe attacks, we may speculate that sporadic cases have been exposed to stronger or multiple environmental factors resulting in more frequent and longer attacks, considering the environmental component of migraine previously has been estimated to be around 54%.[1] Alternatively, it might simply be that familial migraineurs seek treatment earlier due to their knowledge of migraine from other family members and are thus more likely to receive correct treatment earlier on, resulting in less severe migraine attacks and a lower lifetime frequency of attacks.

The recruitment of all patients in the study was done at the same tertiary specialized headache center avoiding selection bias. Data have been collected over many years, using the same validated semi-structured interview with adaptions over the years. Further, the interviews were conducted by a trained physician or senior medical student. In regards to the diagnosis of migraine, the semi-structured interview has a sensitivity of 99%, a specificity of 86% and kappa statistics of 0.89 compared to the gold standard clinical interview performed by a physician.[12] This ensures a high degree of continuity and validity when comparing the data.

We recognized that, although using structured interviews the data are retrospective which could affect the generalization of the study.[13] Furthermore, as patients were recruited from a tertiary headache center, generalizing the results to other than similar clinical populations should be done with caution, and the interpretation must be made in the contexts of the fact that these patients were recruited during different time windows. All patients included were asked if they had any first-degree relatives with migraine, and if they said yes, interviews of the family members were performed to ensure the diagnosis. Interviews on relatives were done to ensure the migraine diagnosis of familial migraineurs, however interviews were not performed on relatives to sporadic migraineurs, thus we cannot exclude some incidences of unknown familial migraine could exist. However, our experience is that families are generally very well informed about other family members having migraine.

Additionally, we did not asses second-degree relatives, thus we cannot exclude the possibility that a recessive inheritance pattern of migraine exists, even though migraine is suggested to be of additive genetic nature.[14] Finally, migraine with and without aura in familial and sporadic incidences were not equally distributed, thus the distribution of migraine with and

without aura may not reflect a clinical setting as recruitment was focused on patients with aura in the first wave of recruitment.

CONCLUSION

The results from this study suggest that sporadic migraineurs have been exposed to stronger or multiple environmental factors due to the higher incidence of severe migraine. This can also be of clinical relevance, as the physician can take this into account and aim to prevent severe migraine, especially in sporadic migraineurs. This study underlines the fact that headache characteristics, triptan response, and comorbidities are similar whether the migraine is inherited or not and thus a homogenous disease.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

Julie Ravn, Mona A. Chalmer, and Thomas F. Hansen

(b) Acquisition of Data

Julie Ravn, Mona A. Chalmer, and Emil L. Oehrstroem

(c) Analysis and Interpretation of Data

Julie Ravn, Lisette J. A. Kogelman, and Thomas F. Hansen

Category 2

(a) Drafting the Manuscript

Julie Ravn and Emil L. Oehrstroem

(b) Revising It for Intellectual Content

Thomas F. Hansen, Mona A. Chalmer, and Lisette J. A. Kogelman

Category 3

(a) Final Approval of the Completed Manuscript

Julie Ravn, Mona A. Chalmer, Emil L. Oehrstroem, Lisette J. A. Kogelman, and Thomas F. Hansen

REFERENCES

1. Mulder EJ, Van Baal C, Gaist D, et al. Genetic and environmental influences on migraine: A twin study across six countries. *Twin Res*. 2003;6:422-431.
2. Ziegler DK, Hur YM, Bouchard TJ, Jr., Hassanein RS, Barter R. Migraine in twins raised together and apart. *Headache*. 1998;38:417-422.
3. Russell MB, Olesen J. Increased familial risk and evidence of genetic factor in migraine. *BMJ*. 1995;311: 541-544.
4. Rainero I, Valfre W, Gentile S, et al. A comparison of familial and sporadic migraine in a headache clinic population. *Funct Neurol*. 2002;17:193-197.
5. Pelzer N, Louter MA, van Zwet EW, et al. Linking migraine frequency with family history of migraine. *Cephalalgia*. 2019;39:229-236.
6. Eriksen MK, Thomsen LL, Andersen I, Nazim F, Olesen J. Clinical characteristics of 362 patients with familial migraine with aura. *Cephalalgia*. 2004;24: 564-575.
7. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.
8. Esserlind AL, Christensen AF, Le H, et al. Replication and meta-analysis of common variants identifies a genome-wide significant locus in migraine. *Eur J Neurol*. 2013;20:765-772.
9. Rasmussen BK, Jensen R, Olesen J. Questionnaire versus clinical interview in the diagnosis of headache. *Headache*. 1991;31:290-295.
10. Gervil M, Ulrich V, Olesen J, Russell MB. Screening for migraine in the general population: Validation of a simple questionnaire. *Cephalalgia*. 1998;18:342-348.
11. Esserlind AL, Christensen AF, Steinberg S, et al. The association between candidate migraine susceptibility loci and severe migraine phenotype in a clinical sample. *Cephalalgia*. 2016;36:615-623.
12. Kirchmann M, Seven E, Bjornsson A, et al. Validation of the deCODE migraine questionnaire (DMQ3) for use in genetic studies. *Eur J Neurol*. 2006;13:1239-1244.
13. Hudson JI, Pope HG, Jr., Glynn RJ. The cross-sectional cohort study: An underutilized design. *Epidemiology*. 2005;16:355-359.
14. Gormley P, Anttila V, Winsvold BS, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. *Nat Genet*. 2016;48:856-866.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.