Prevalence of lifetime depression in a large hemiplegic migraine cohort

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ABSTRACT

Objective: To determine the prevalence of depression and determinants associated with depression in a large population of hemiplegic migraine (HM) patients.

Methods: We conducted a cross-sectional, validated questionnaire study among 89 well-defined HM patients and 235 headache-free controls. The prevalence of lifetime depression and its relation to migraine characteristics was assessed.

Results: HM patients had increased odds for lifetime depression (odds ratio 3.73, 95% confidence interval 2.18–6.38) compared with controls. Use of acute antimigraine medication was associated with lifetime depression.

Conclusions: Depression is part of the monogenic hemiplegic migraine phenotype. Further studies are needed to elucidate the pathophysiologic role of HM genes in comorbid depression. For now, clinicians should take comorbid depression into consideration when starting prophylactic treatment of HM. ***Neurology*® 2016;87:2370–2374**

GLOSSARY

CES-D = Center for Epidemiologic Studies Depression Scale; **GEE** = generalized estimating equation; **HADS** = Hospital Anxiety and Depression Scale; **HM** = hemiplegic migraine.

Hemiplegic migraine (HM) is a rare autosomal dominantly inherited migraine subtype, characterized by motor weakness during the aura phase.[1] Three genes (*CACNA1A*, *ATP1A2*, and *SCN1A*) have so far been associated with HM. Involvement of a fourth gene (*PRRT2*) in HM has been proposed, but further evidence is needed to support this claim.[2] HM is divided into 2 subtypes: familial HM, in which at least one first- or second-degree relative has HM, and sporadic HM, in which no first- or second-degree relative is affected.

The relationship between the common types of migraine and depression has been thoroughly investigated to identify shared etiologic factors. Bidirectional associations have been proven, suggesting shared genetic risk factors.[3,4] As a monogenic migraine subtype, HM constitutes a more homogeneous model to study migraine pathophysiology than migraine subtypes with a complex genetic background (such as migraine with and without aura). In HM, prevalence of depression has only been studied on a very small scale.[5] It has been hypothesized that the core pathophysiologic mechanisms are similar for HM and other types of migraine, with HM representing the severe end of the phenotypic migraine spectrum. If there is a direct relationship between migraine and depression, one could hypothesize that HM, as a more severe migraine phenotype, may be associated with at least an equal prevalence of depression compared to patients with common migraine subtypes. Even more, an increased prevalence of depression in HM may suggest an involvement of ion channels that are mutated in HM in the pathophysiology of (certain subtypes of) depression.

In this study, we studied the prevalence of lifetime depression in HM and the clinical determinants associated with depression in a unique large population of HM patients.

Supplemental data at Neurology.org

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METHODS

Participants. HM patients of Dutch origin were recruited from the HM research database of the Leiden University Medical Center including patients who visited our outpatient headache clinic or were interviewed by an experienced research-physician (N.P.) or neurologist (G.M.T.). Patients were ineligible to participate when aged <18 years or when unable to fill in the questionnaires (e.g., due to mental retardation or cognitive decline). Healthy individuals willing to participate had to pass a screening and additional questionnaire online via the research website of the Leiden University Migraine Neuro-Analysis program (LUMINA).[6] If participants did not report any symptoms of migraine, cluster headache, chronic tension-type headache, or medication overuse headache, they were considered as nonheadache healthy controls. These healthy controls were also sent web-based questionnaires on symptoms of (lifetime) depression and demographic characteristics identical to the questionnaires that were sent to the HM patients.

Standard protocol approvals, registrations, and patient consents. The study was approved by the medical ethics committee of Leiden University Medical Center and all participants provided informed consent.

Measurements. Symptoms of depression were determined using validated cutoff scores for the Hospital Anxiety and Depression Scale (HADS) and the Center for Epidemiologic Studies Depression Scale (CES-D).[7,8] The HADS questionnaire has been used in clinical studies as it intrinsically corrects for the overlap between symptoms of somatic diseases and depression (e.g., lack of sleep, changes in appetite). Lifetime depression was defined as HADS-D ≥8 or CES-D ≥16 or (past) depression diagnosed by a physician or (past) use of antidepressants for depression. The combination of current depression questionnaires and lifetime depression questions allowed for analyses on both lifetime and current depression. Current depression was defined as HADS-D ≥8 and current anxiety was defined as HADS-A ≥8. Information about headache frequency and antimigraine medication use was collected via an additional questionnaire. Healthy controls were sent the same depression questionnaires as the HM patients.

Data analysis. General characteristics were reported as medians (interquartile range) or percentages. To take into account that some of the HM cases were family-related (originating from 18 separate families), we used generalized estimating equations (GEE) regression, which can correct for this confounding. GEE was applied to study the prevalence of depression corrected for sex, age, and the presence of related individuals. GEE regression was also used in the analysis of determinants associated with depression in HM patients. A p value of <0.05 was considered statistically significant. All analyses were performed with SPSS 20.0 (SPSS Inc., IBM, Armonk, NY).

RESULTS

Study population. We included 89 participants with HM and 235 healthy controls in the study (figure). From 132 HM participants in the database, 20 were ineligible because of previously stated unwillingness to participate in further research (n = 1) or outdated contact information (n = 19), and 23 decided not to participate (19 familial HM, 4 sporadic HM). No differences were observed between participants (n = 89) and nonparticipants (n = 43) in age or sex. Differences in headache frequency and medication use between participants and nonparticipants could not be tested because of missing data in the nonparticipants. Information on genetic status was missing for 3 patients, and in 10 patients genetic screening was incomplete.

Comparing HM patients with controls. The prevalence of lifetime depression was 51.7% in HM patients compared to 21.3% in controls (table 1). In multivariate analysis, with correction for sex and for the fact that multiple participants belonged to shared families, a strong association with lifetime depression was established (table 2).

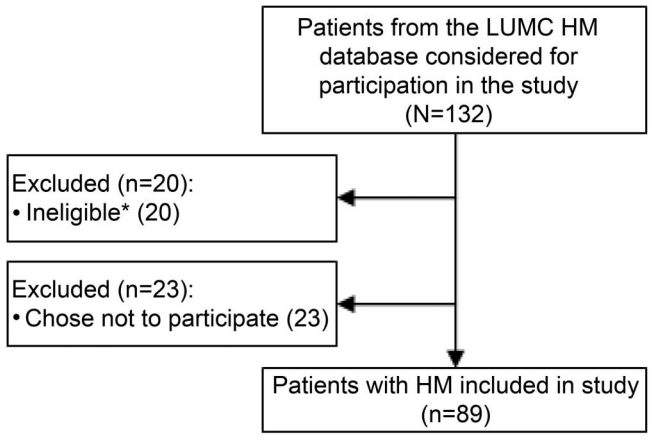
Comparing HM patients with and without lifetime depression. HM patients with lifetime depression did not differ from patients without lifetime depression in sex, age, HM type, or mutation status (table 3). Migraine attack frequency tended to be higher in the depression group. Use of acute antimigraine medication (also when analyzed separately for analgesics and triptans) was increased in patients with depression. Finally, current anxiety appeared highly comorbid with depression.

DISCUSSION

We studied the prevalence of lifetime depression in HM, a rare monogenic subtype of migraine. We found, like in the common types of migraine, a 4 times increased odds compared with controls.

In a previous study, using the same methodology and questionnaires to diagnose depression, we found a comparable prevalence of 45% for lifetime depression in the common types of migraine.[9] Migraine attacks with typical aura (without weakness) frequently occur in HM patients.[10] Therefore, the comorbidity of HM with depression could, at least partly, be due to presence of common types of

Figure Flowchart study population



*Patients were ineligible if they had previously indicated that they did not want to be contacted for scientific research or if no current contact information was available. HM = hemiplegic migraine; LUMC = Leiden University Medical Center.

Table 1 Sociodemographic and clinical characteristics

	HM participants (n = 89)	Controls (n = 235)
Female sex, n (%)	66 (74.2)	138 (58.7)
Age, y, median (IQR) (range)	46 (24) (20-70)	48 (24) (19-77)
FHM, n (%)	65 (73.0)	—
HADS-A, median (IQR) (range)	5 (6) (0-17)	3 (3) (0-17)
HADS-D, median (IQR) (range)	4 (5) (0-12)	2 (3) (0-16)
CES-D, median (IQR) (range)	11 (15) (0-55)	4 (7) (0-41)
Lifetime depression present, n (%)	46 (51.7)	50 (21.3)
Current depression present, n (%)	36 (40.4)	29 (12.3)
Current anxiety present, n (%)	32 (36.0)	24 (10.2)

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale; FHM = familial hemiplegic migraine; HADS-A = Hospital Anxiety and Depression Scale-anxiety; HADS-D = Hospital Anxiety and Depression Scale-depression; HM = hemiplegic migraine; IQR = interquartile range. Current depression: HADS-D ≥8. Current anxiety: HADS-A ≥8. Comparison of HM participants and controls.

migraine in our HM patients. Elaborate migraine characteristics were not included in the questionnaires used in this study. It would, however, have been difficult to exclude common types of migraine, as the included HM patients may still develop such attacks. We therefore cannot provide exact figures on the prevalence of the common types of migraine in our population.

Depression in common migraine is strongly associated with migraine attack frequency and is a risk factor for chronification.[9] Due to the small number of HM patients, we could not show an association with attack frequency. However, use of acute antimigraine medication (simple analgesics and triptans) was associated with depression. Considering increased use of acute antimigraine medication as a proxy for migraine severity, the association may not be dependent on attack frequency, but on the severity of accompanying migraine symptoms.

The lifetime prevalence of depression of 21% in the control population corresponds to published prevalence rates for depression,[11] indicating that our measurement of lifetime depression appears accurate.

Table 2 Generalized estimating equation regression with odds of lifetime depression

	Univariate OR	95% CI	p Value	Multivariate OR	95% CI	p Value
Presence of HM	4.04	2.38-6.88	<0.001	3.73	2.18-6.38	<0.001[a]
Sex (female vs male)	2.18	1.28-3.70	0.004	1.90	1.09-3.30	0.023[a]
Age	0.99	0.97-1.01	0.19	—	—	—

Abbreviations: CI = confidence interval; HM = hemiplegic migraine; OR = odds ratio.
[a] Significant.

HM patients showed increased anxiety, which might have contributed to the increased comorbid prevalence of depression. Unraveling the exact role of anxiety should be a topic for future research. A possible limitation of the study is the fact that some of the patients are related to other individuals in the study, because HM families were included. However, it turned out that many different families participated, but each only contributed a few individuals (table e-1 at Neurology.org). Furthermore, we performed a GEE analysis to correct for this possible bias. It should be noted that we did multiple statistical tests but kept the level of significance at 0.05, as is consistent with an exploratory study.

Although recent molecular genetic advances have provided insights into pathophysiologic mechanisms of inherited channelopathies such as HM, so far no relationship with depression has been shown or investigated. Extensive biophysical characterization in representative model systems will be required to determine the contribution of different ion channel variants to the common types of migraine in general and the comorbidity with depression.[12]

Because of the cross-sectional design of our study, we can only speculate on the mechanism of action of the comorbidity between HM and depression. Our results may indicate that the genes involved in HM may, directly or indirectly, make patients more susceptible to depression. It would be interesting to study the role of ion channels encoded by *CACNA1A*, *ATP1A2*, and *SCN1A* in large cohorts with comorbid depression and common forms of migraine. The high prevalence of depression in our HM cohort also may have clinical implications. HM patients should be screened for depression, and migraine prophylactics such as flunarizine or topiramate, which may provoke depressive symptoms, should perhaps be prescribed with caution in HM patients with active depression.[13]

Depression is part of the monogenic HM phenotype. This increased risk of depression in HM patients should receive more attention in clinical practice, especially with regard to the choice of prophylactic antimigraine medication. In addition, further studies are needed to elucidate the pathophysiologic role of HM genes in comorbid migraine and depression.

AUTHOR CONTRIBUTIONS

M.A. Louter is principal investigator and contributed to design and conceptualization of the study, data collection, analysis and interpretation, as well as writing the first draft of the manuscript together with N.P. and I.B. and revising. N. Pelzer contributed to design and conceptualization of the study, data collection, analysis and interpretation, as well as writing the first draft of the manuscript together with M.A.L. and I.B. and revising. I. de Boer contributed to analysis and interpretation of the data, as well as writing the first draft of the manuscript together with M.A.L. and N.P. E.C. Kuijvenhoven contributed to data collection, as well as revising the manuscript for intellectual content. W.P.J. van Oosterhout contributed to data collection, as well

Table 3 Comparison of hemiplegic migraine (HM) participants with and without lifetime depression

	HM without lifetime depression (n = 43)	HM with lifetime depression (n = 46)	Univariate OR	95% CI	p Value[a]
Female sex (female vs male), n (%)	32 (74.4)	34 (73.9)	0.97	0.40–2.37	0.95
Age, y, median (IQR) (range)	48.0 (25) (22–70)	44.5 (24) (23–69)	1.0	0.95–1.03	0.61
Migraine attack frequency, n (%)[b]			—	—	0.23[c]
Over 1 year ago	15 (38.5)	6 (14.3)	—	—	R
1–2 attacks per year	14 (35.9)	17 (40.5)	—	—	—
3–6 attacks per year	4 (10.3)	8 (19.0)	—	—	—
7–12 attacks per year	3 (7.7)	6 (14.3)	—	—	—
13–54 attacks per year	1 (2.6)	4 (9.5)	—	—	—
>54 per year	2 (5.1)	1 (2.4)	—	—	—
Use of acute medication, n (%)[b,d]			—	—	0.008[e]
No	23 (59.0)	11 (26.2)	—	—	R
Yes, only when attack starts	13 (33.3)	25 (59.5)	4.10	1.69–9.98	0.002[e]
Yes, (almost) daily	3 (7.7)	6 (14.3)	2.39	0.54–10.7	0.25
Use of standard analgesics[d]					
Yes (R = no), n (%)	19 (48.7)	32 (76.2)	3.42	1.55–7.54	0.002[e]
Days per month, median (IQR)	1.00 (8)	6.50 (10)	1.05	0.98–1.12	0.19
Use of triptans[b,d]					
Yes (R = no), n (%)	7 (17.9)	17 (40.5)	3.15	1.32–7.52	0.01[e]
Days per month, median (IQR)	0.00 (0)	0.00 (2)	1.36	0.89–2.08	0.16
Use of prophylactic medication, n (%)[b,d]					
Yes (R = no)	14 (35.9)	14 (33.3)	0.88	0.32–2.45	0.81
FHM (R = SHM)	32 (74.4)	33 (71.7)	0.90	0.29–2.81	0.78
Mutation status, n (%)[f]			—	—	0.53
No mutation found	19 (48.7)	22 (59.5)	—	—	R
CACNA1A mutation	9 (23.1)	7 (18.9)	—	—	—
ATP1A2 mutation	11 (28.2)	8 (21.6)	—	—	—
SCN1A mutation	0 (0)	0 (0)	—	—	—
Current anxiety present (R = no)	4 (9.3)	28 (60.9)	17.5	5.34–57.4	<0.001[e]

Abbreviations: CI = confidence interval; FHM = familial hemiplegic migraine; GEE = generalized estimating equation; IQR = interquartile range; OR = odds ratio; R = reference category in generalized estimating equation; SHM = sporadic hemiplegic migraine.
[a] Corrected for multiple individuals from the same family.
[b] Without lifetime depression n = 39 and lifetime depression n = 42 (due to missing data).
[c] GEE regression performed with category 13–54 attacks per year and >54 per year merged because of small numbers. The Fisher exact test using all categories gave a *p* value of 0.13.
[d] Questions specifically stated analgesics for severe headache.
[e] Statistically significant.
[f] No lifetime depression group n = 39 and lifetime depression group n = 37 (due to missing data).

as revising the manuscript for intellectual content. E.W. van Zwet contributed to analysis and interpretation of the data. M.D. Ferrari contributed to interpretation of the data, as well as revising the manuscript for intellectual content. G.M. Terwindt contributed to design and conceptualization of the study, interpretation of the data, as well as revising the manuscript for intellectual content.

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DISCLOSURE

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