The migraine triad: chronification, depression, and medication overuse

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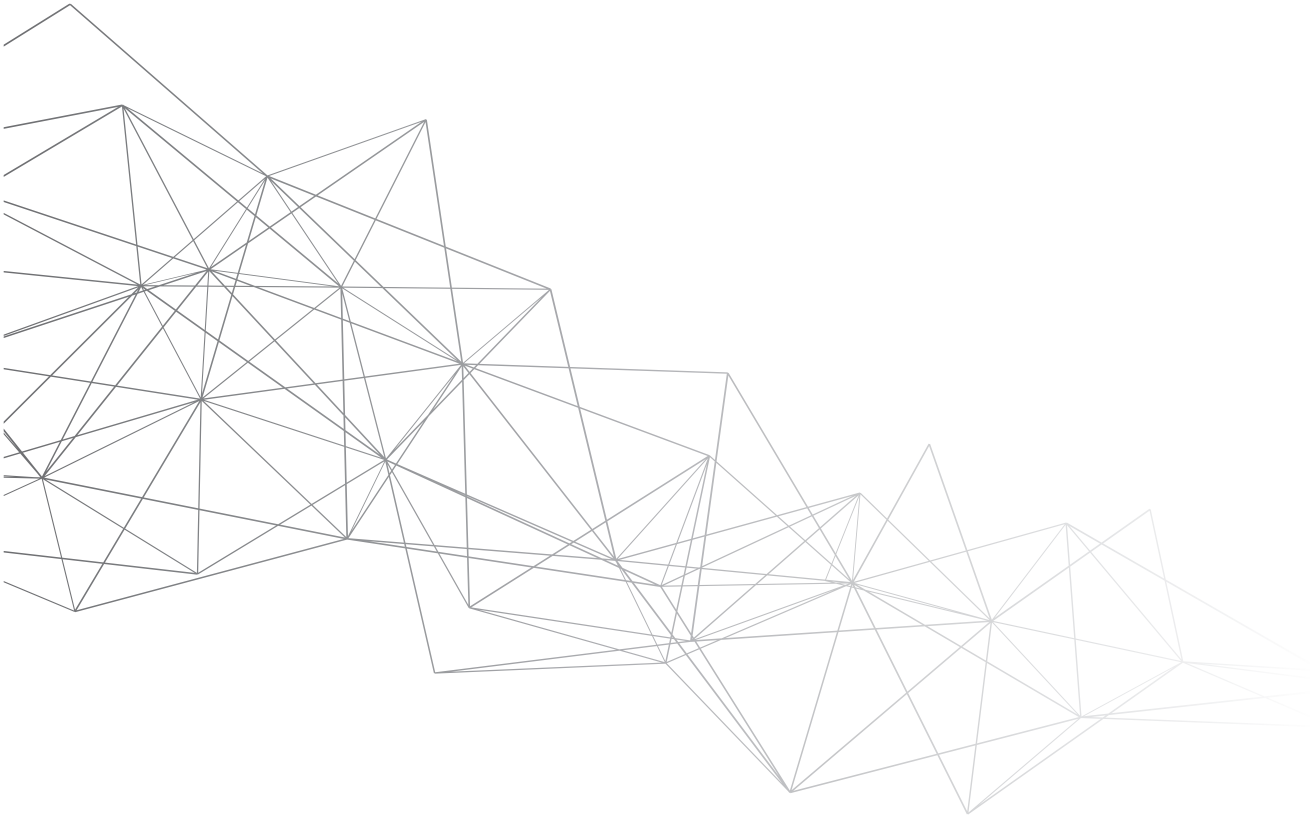
2 CHAPTER

Allodynia is associated with a higher prevalence of depression



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Abstract

Introduction
There is a strong association between migraine and depression. The aim of this study was to identify migraine specific factors involved in this association.

Methods
We conducted a cross-sectional study in a large well-defined cohort of migraine patients (n=2533). We assessed lifetime depression using validated questionnaires, and diagnosed migraine based on the International Classification of Headache Disorders III-beta criteria. Multivariate regression analyses were conducted.

Results
Of the 2533 migraineurs that were eligible, 1137 (45%) suffered from lifetime depression. The following independent factors were associated with an increased depression prevalence: i) migraine specific risk factors: high migraine attack frequency, the presence of allodynia, ii) general factors: being a bad sleeper, female gender, high BMI, being single, smoking, and a low alcohol consumption.

Conclusion
This study identified allodynia, in addition to high migraine attack frequency, as a new migraine specific factor associated with depression.

Introduction

Migraine and depression both rank among the most prevalent and disabling disorders and show a bidirectional increased comorbidity. (1-4) Such bidirectional association suggests a shared aetiology, which is at least partly explained by genetic factors. (5, 6)

Comorbid depression seems to be particularly common in chronic migraine patients. (7) Depression is also an important predictor of medication overuse, which is seen in up to half of persons with chronic migraine. (8) Comorbid depression is thus likely to increase the risk of chronification in migraine and to complicate treatment. (9-11) In addition, comorbid migraine is associated with poorer functioning and increased somatic complaints in depressed patients. (12) Altogether, a triad is suggested of migraine chronification, depression and medication overuse. Identifying migraine specific factors associated with depression will help to detect patients that are at an increased risk of depression and chronification.

The aim of this study was to further elucidate the association between migraine and depression in a large, well-defined, web-based migraine cohort and to identify migraine specific factors associated with depression.

Methods

Participants and procedures

Our study was conducted as a part of the LUMINA project. (13) Participants of the LUMINA project were Dutch adults aged 18 to 74 years with migraine with or without aura according to the International Classification of Headache Disorders criteria (previously ICHD-II, now ICHD-III beta version). The LUMINA project was approved by the medical ethics committee of the Leiden University Medical Centre. All subjects provided written informed consent prior to the study. For a further description of the participants and procedures, see Supplementals.

Measures

Lifetime depression was measured, using validated cut-off scores on depression questionnaires and additional questions on lifetime depression. (14, 15) Cutaneous allodynia was measured using the 12-item Allodynia Symptom Checklist. The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep disturbances during the month before assessment. (16) For a further description of the measures, see Supplementals.

Data analysis

Logistic regression analyses were used to test which variables were associated with lifetime depression among migraine patients. For all analyses *p*-values of <0.05 were considered to indicate statistical significance. For an extended description of the data analyses, see Supplementals.

Results

Study population and descriptive statistics

The total study flow is shown in supplemental fig. 1. In total, 3624 migraineurs within the LUMINA project were sent a depression questionnaire (mean age: 41.7 ± 11.9), based on migraine diagnosis and the presence of written informed consent. In total 3177 (87.7%) returned this depression questionnaire. Because of missing data, 2533 were eventually included in the analysis.

Comparison of included vs. excluded participants showed for all analyses that included participants were slightly older and had more often migraine with aura, but did not differ in gender (data not shown). Of the 2533 migraineurs that were eligible 1137 (45%) suffered from life time depression. A total of 1767 migraine patients (70%) suffered from allodynia during migraine attacks.

Correlates of depression in migraine patients

The comparison for migraine patients with depression versus those without depression is shown in Table 1. The results of the initial univariate analyses are shown in Table 2 (left part). Significant univariate associations with depression were found for the following migraine specific variables: attack frequency, number of migraine days, use of prophylactic medication and allodynia. Other statistically significant variables were being a bad sleeper, gender, BMI, level of education, marital status, smoking, and alcohol consumption. These variables (except number of migraine days, because of the high correlation with migraine attack frequency) were entered together in a multivariate logistic regression analysis. The results of this analysis (Table 2, right part) showed the following independent factors associated with depression in migraine patients; i) the migraine specific factors: high migraine attack frequency, allodynia, ii) the general factors: being a bad sleeper, female gender, high BMI, being single, smoking, and alcohol consumption.

Discussion

This large-scale study in a well-defined migraine cohort showed that depression is associated with allodynia and high attack frequency in migraine patients. Our study is the first large, web-based study to show that allodynia is associated with an increased prevalence of depression in migraine patients. Previous studies investigated the reversed association, namely that the risk of allodynia is higher among migraine patients with depressive symptoms. (17, 18) One recent, small clinic-based study showed that the severity of cutaneous allodynia was associated with current mood status, but did not focus on lifetime depression. (19) Thus, according to our study and others, migraine, depression and allodynia are intertwined. In a previous study we showed that allodynia (and depression) make a migraine patient vulnerable for migraine chronification. (20) Since 70% of migraineurs suffer from allodynia, the clinical impact of this finding might be limited. However, the pathophysiological role of allodynia in migraine chronification and the migraine-depression association is of great importance. Allodynia is considered as a clear marker for a central sensitization process of the brain. (21) Central sensitization is an activity-dependent functional plasticity that results from post-translational regulation and transcriptional regulation of key gene products. (22) Once established, sensitization of second order trigeminovascular neurons becomes activity independent, and maintains itself in the absence of sensory input later on. Clinically, central sensitization causes refractoriness to acute treatment. (21) Thus, allodynia has consequences for disease progression and treatment, and it should lead to an increased awareness of comorbidity of migraine and depression, and of risk of chronification of migraine. Pathophysiologically, the triad migraine, depression and allodynia may suggest a self-reinforcing dysfunction of CNS structures involved in the modulation of neuronal excitability and pain.

Poor sleep quality in migraine patients was associated with higher odds of depression. Whereas the hypothalamus is supposedly involved in migraine, depression, and sleep disorders, the association between these three disorders is suggestive of hypothalamic modulation of the trigeminovascular pathway. (23) Pain signals that originate in the trigeminovascular pathway can alter the activity of hypothalamic and limbic structures that integrate sensory, physiological and cognitive signals that drive behavioural, affective and autonomic responses. (24)

The strengths of this study are the large sample size, the well-defined migraine status and detailed information on depression characteristics. Most importantly, this is one of the first studies demonstrating that cutaneous allodynia and sleep disturbances are strongly associated with depression in migraineurs. Possible limitations include the fact that our population might be younger and higher educated than the migraine population in general due to the recruitment of patients via the internet. However, we tried to limit this effect by enabling participants to fill

out the questionnaires on paper. The cross-sectional nature of this study prevented us from drawing conclusions about causality in the relationship between high attack frequency, allodynia, sleep disturbances and depression.

In summary, frequent attacks and allodynia are associated with a higher prevalence of depression in migraine patients. Future research should focus on identifying pathophysiological mechanisms linking migraine and depression.

Tables and figures

Table 1: Baseline characteristics LUMINA population of 2533 migraine patients, separated by the presence of lifetime depression.

	No lifetime depression n = 1396	Lifetime depression n = 1137
Migraine specific variables		
Age at onset migraine	19.4 ± 10.2	19.5 ± 10.9
Migraine type		
MO	856 (61.3%)	702 (61.7%)
MA	540 (38.7%)	435 (38.3%)
Migraine attack frequency		
1-2 attacks per year	71 (5.1%)	31 (2.7%)
3-6 attacks per year	206 (14.8%)	152 (31.4%)
7-12 attacks per year	448 (32.1%)	306 (26.9%)
13-54 attacks per year	577 (41.3%)	517 (45.5%)
more than 54 attacks per year	94 (6.7%)	131 (11.5%)
Number of migraine days		
1-2 days per year	86 (6.2%)	44 (3.9%)
3-6 days per year	150 (10.7%)	93 (8.2%)
7-12 days per year	261 (18.7%)	178 (15.7%)
13-54 days per year	666 (47.7%)	516 (45.4%)
more than 54 days per year	233 (16.7%)	306 (26.9%)
Use of acute medication		
no	119 (8.5%)	112 (9.9%)
yes, if attack	1114 (79.8%)	844 (74.2%)
yes, (almost) daily	163 (11.7%)	181 (15.9%)
Use of a triptan (yes)	998 (71.5%)	835 (73.4%)
Use of prophylactic medication (yes)	483 (34.6%)	482 (42.4%)
Allodynia (yes)	913 (65.4%)	854 (75.1%)
General variables		
Gender (female)	1168 (83.7%)	1001 (88.0%)
Age (years)	44.1 ± 11.6	44.8 ± 11.5
BMI (kg/m^2)	24.4 ± 3.9	24.8 ± 4.4
Years of fulltime education	13.8 ± 3.3	13.4 ± 3.5
Marital status		
Single	194 (13.9%)	215 (18.9%)
Cohabiting / married	1143 (81.9%)	821 (72.2%)
Divorced / widowed	59 (4.2%)	101 (8.9%)
Smoking packyears	4.1 ± 8.2	5.7 ± 9.8
Caffeine consumption (ie per day)	6.0 ± 3.0	5.7 ± 2.8
Alcohol consumption (ie per week)	3.0 ± 3.9	3.4 ± 3.7
Bad sleeper (yes)	799 (57.2%)	890 (78.3%)

BMI, body mass index; MO, Migraine without aura; MA, Migraine with aura.
Values are the absolute numbers with corresponding percentages or means ± SD.
Few (n=35) patients reported more than one attack on one day, probably because migraine recurrences were counted as new attacks

Table 2: Logistic associations between patient characteristics and the odds of lifetime depression: a model for depression in 2533 persons with migraine.

	Univariate OR	95% CI	p-value	Multivariate OR	95% CI	p-value
Migraine specific variables						
Age at onset migraine	1.00	0.99 – 1.01	0.78	.	.	.
Migraine type (MA vs. MO)	1.02	0.87 – 1.20	0.83	.	.	.
Migraine attack frequency						
3-6 vs. 1-2 attacks per year	**1.69**	**1.06 – 2.71**	**0.03**	1.51	0.92 – 2.47	0.10
7-12 vs. 1-2attacks per year	**1.56**	**1.00 – 2.44**	**0.05**	1.35	0.85 – 2.16	0.21
13-54 vs. 1-2 attacks per year	**2.05**	**1.32 – 3.18**	**0.001**	**1.72**	**1.08 – 2.75**	**0.02**
more than 54 vs. 1-2 attacks per year	**3.19**	**1.94 – 5.25**	**<0.001**	**2.30**	**1.36 – 3.92**	**0.002**
Number of migraine days						
3-6 vs. 1-2 days per year	1.21	0.78 – 1.89	0.40	.	.	.
7-12 vs. 1-2 days per year	1.33	0.88 – 2.01	0.17	.	.	.
13-54 vs. 1-2 days per year	**1.51**	**1.04 – 2.22**	**0.03**	.	.	.
> 54 vs. 1-2 days per year	**2.57**	**1.72 – 3.83**	**<0.001**	.	.	.
Use of acute medication						
yes, if attack vs. no	0.81	0.61 – 1.06	0.12	.	.	.
yes, (almost) daily vs. no	1.18	0.85 – 1.65	0.33	.	.	.
Use of a triptan (yes vs. no)	1.10	0.93 – 1.31	0.28	.	.	.
Use of prophylactic medication (yes vs. no)	**1.39**	**1.18 – 1.63**	**<0.001**		0.94 – 1.33	0.23
Allodynia (yes vs. no)	**1.60**	**1.34 – 1.90**	**<0.001**		**1.05 – 1.52**	**0.02**

	Univariate OR	95% CI	p-value	Multivariate OR	95% CI	p-value
General variables						
Gender (female vs. male)	**1.44**	**1.14 – 1.81**	**0.002**	**1.29**	**1.00 – 1.65**	**0.05**
Age (years)	1.01	1.00 – 1.01	0.16	.	.	.
BMI (kg/m^2)	**1.03**	**1.01 – 1.05**	**0.007**	**1.02**	**1.00 – 1.04**	**0.04**
Years of fulltime education	**0.97**	**0.94 – 0.99**	**0.004**	0.98	0.96 – 1.01	0.20
Marital status						
Cohabiting / married vs. single	**0.65**	**0.52 – 0.80**	**<0.001**	**0.66**	**0.53 – 0.82**	**<0.001**
Divorced / widowed vs. single	**1.55**	**1.06 – 2.25**	**0.02**	1.29	0.87 – 1.91	0.20
Smoking packyears	**1.02**	**1.01 – 1.03**	**<0.001**	**1.02**	**1.01 – 1.03**	**<0.001**
Caffeine consumption (ie per day)	0.98	0.95 – 1.00	0.07	.	.	.
Alcohol consumption (ie per week)	**0.96**	**0.94 – 0.98**	**<0.001**	**0.97**	**0.95 – 0.99**	**0.01**
Bad sleeper (yes vs. no)	**2.69**	**2.26 – 3.21**	**<0.001**	**2.34**	**1.95 – 2.81**	**<0.001**
Constant				**0.19**	.	**<0.001**

BMI, body mass index; MO, Migraine without aura; MA, Migraine with aura.
Data are Odds Ratios with 95% confidence intervals and *p*-values. In the univariate analysis all predictors were tested separately. Only the variables with a $p < 0.05$ in the univariate analysis were used as covariates in the multivariate analysis. Values depicted in bold indicate a statistical significant results at the .05 level.

Supplementals

Methods

Participants and procedures

Our study was conducted as a part of the LUMINA project. (13) Participants of the LUMINA project were Dutch adults aged 18 to 74 years with migraine with or without aura according to the International Classification of Headache Disorders criteria (previously ICHD-II, now ICHD-III beta version).

Our LUMINA study population was invited via the lay press nationwide to enroll via the especially designed, nation-wide LUMINA website. Additionally, patients from our outpatient headache clinic were invited by a letter. This group however, comprises only 3.5% of the total LUMINA population. On the website, patients were asked to fill out a screening questionnaire that has been validated previously. (25) Firstly, if patients fulfilled the screening criteria, they were sent a web-based extended migraine questionnaire, based on the ICHD-II criteria (now ICHD-III beta). (14, 15, 26) This questionnaire was validated by performing a semi-structured telephone interview in 1038 patients who had filled out the extended migraine questionnaire. (13) The specificity of the questionnaire was 0.95. In addition to questions that were necessary to diagnose migraine accurately, the extended questionnaire also included items on demographic factors, acute and prophylactic headache medication use, migraine attack frequency and migraine days, and allodynia (the experience of pain due to stimuli that do normally not provoke pain). Participants without the needed internet skills were able to fill out the questionnaires on paper.

Secondly, a web-based questionnaire on symptoms of (lifetime) depression was submitted to all migraine patients (n=3624). This depression questionnaire consisted of the Hospital Anxiety and Depression Scale (HADS-D), the Centre for Epidemiologic Studies Depression Scale (CES-D) and additional questions on lifetime depression: 'Have you ever used anti-depressants, prescribed for a depression?' and 'Have you ever been diagnosed with a depression'? (14, 15) Lastly, a questionnaire was sent to all participants for details on sleeping disturbances, to be able to adjust for the potential confounding effect of sleep in the relationship between migraine and depression.

The LUMINA project was approved by the medical ethics committee of the Leiden University Medical Centre. All subjects provided written informed consent prior to the study.

Measures

Lifetime depression diagnoses were based on extended and validated questionnaires, according to the International Classification of Headache Disorders (previously ICHD-II, now ICHD-III beta version). (13, 25, 26) Migraine frequency was measured both as attacks per year and as migraine days per year, using 5 categories: 1-2 attacks/days per year, 3-6 attacks/days per year, 7-12 attacks/days per year, 13-54 attacks/days per year, more than 54 attacks/days per year.

Lifetime depression was measured as a dichotomous variable. We used validated cut-off scores, in combination with a previously used and published algorithm for depression and an additional question on lifetime depression: (lifetime depression = HADS-D ≥ 8 *or* CESD ≥ 16 *or* use of antidepressants (prescribed for a depression) *or* diagnosis depression). (6, 14, 15) Although the HADS-D (depression subscale of the HADS) and CESD questionnaires focused only on the previous two weeks, we aimed to reliably measure lifetime depression by adding questions on antidepressant use and depression diagnoses. Validation of the resulting compound depression diagnoses by performing a telephonic Composite International Diagnostic Interview (CIDI) in a subset of 102 randomly selected patients showed a sensitivity of 78% and a specificity of 64% for DSM-IV classified depression. (27)

To assess cutaneous allodynia, the 12-item Allodynia Symptom Checklist (ASC) was used. (17) The ASC was modified to include dichotomous answer options ('yes' and 'no'), which could be counted up to an allodynia score (range: 0-12). If participants scored two points or more they were classified as having allodynia.

To be able to correct for the potential confounding effect of sleep disorders and possible poor sleep quality, the Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep disturbances during the month before assessment. (16) The PSQI is designed to measure the quality and patterns of sleep in the past month and contains 19 self-rated questions, with a global scoring range of 0 to 21. Higher scores denote a poorer sleep quality. A validated cut-off score of ≥5 was used to separate 'good sleepers' from 'bad sleepers'.

Data analysis

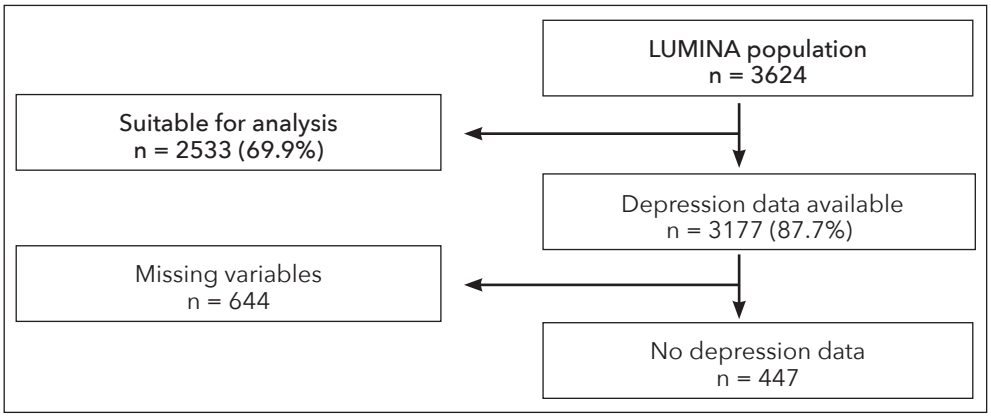
Baseline characteristics were reported as mean (SD) or percentages. Differences in means between groups were tested with independent samples *t*-tests. Differences in proportions were tested by x^2 tests. To determine migraine specific and general determinants of depression, a logistic regression model with lifetime depression as the outcome was developed, using a two-step procedure. First, univariate logistic regression analyses were used to test which potential predictors were associated

with lifetime depression among migraine patients. The following variables were included in the univariate model as migraine specific determinants: age at onset (migraine), migraine subtype, migraine attack frequency, number of migraine days, use of acute medication, use of a triptan, use of prophylactics and allodynia. The following variables were included as general determinants:, gender, age, BMI, educational level, marital status, smoking, caffeine consumption, alcohol consumption, and sleeping disturbances. Second, all predictors with a statistically significant univariate effect were entered in a multivariate logistic regression model. Results were reported as odds ratios with 95% confidence intervals (CI) and corresponding *p*-values.

For all analyses *p*-values of <0.05 were considered to indicate statistical significance. All analyses were performed with SPSS 20.0 (SPSS inc., IBM, USA).

Supplemental Figure 1

Study flow



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