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Associations Between Lipid Levels and Migraine: Cross-sectional Analysis in the EVA Study

Pamela M. Rist, MSc^{1,2}, Christophe Tzourio, MD, PhD^{3,4}, and Tobias Kurth, MD, ScD^{1,2,3,5}

¹Department of Epidemiology, Harvard School of Public Health, Boston, MA

²Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

³INSERM Unit 708—Neuroépidémiologie, Paris, France

⁴University of Bordeaux, Bordeaux, France

⁵UPMC Université Paris 06, UMR_S708, Paris, France

Abstract

Background—Migraine with aura has been associated with increased prevalence of cardiovascular risk factors, including elevated levels of some vascular biomarkers. However, little research has been done on this association among the elderly. We examined the associations of lipid levels with headache and migraine in a cohort of elderly individuals.

Methods—Cross-sectional study among 1155 participants enrolled in the Epidemiology of Vascular Aging Study with available information on headache and blood biomarkers. We used multinomial logistic regression to evaluate the association between biomarker tertiles and headache categories.

Address for correspondence: Tobias Kurth, MD, ScD, INSERM Unit 708 – Neuroepidemiology, Hôpital de la Pitié-Salpêtrière, 47 boulevard de l'Hôpital, 75651 Paris Cedex 13, France, Tel : +33 (0) 1 42 16 25 40; Fax : +33 (0) 1 42 16 25 41, tobias.kurth@univ-bordeaux.fr.

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Results—925 people had no severe headache, 64 people had non-migraine headache, and 166 people had migraine of whom 23 had aura. Compared to participants without headache, we observed strong associations between increasing tertiles of total cholesterol and migraine with aura. The OR (95% CI) was 4.67 (0.99–21.97) for the 2nd tertile and 5.97 (1.29–27.61) for the 3rd tertile. We also found strong associations between triglycerides and migraine with aura (OR for 3rd tertile:4.42 (1.32–14.77).) We did not see significant associations between increased biomarkers levels and any other headache group.

Conclusions—Elevated levels of total cholesterol and triglycerides are associated with migraine with aura but not other headache forms in the elderly.

Keywords

migraine; cholesterol; epidemiology

Migraine is a common recurrent primary headache disorder that has close links to the neuronal and vascular system and is, in some patients, accompanied by transient neurological symptoms mostly of the visual field that are known as migraine aura (1, 2). There is increasing evidence that migraine with aura is associated with increased risk of ischemic stroke (3–6) and other vascular disease events.(7, 8) Furthermore, migraine has been associated with increased prevalence of specific cardiovascular risk factors (9, 10), including some vascular biomarkers (11, 12).

There has been particular interest in the association between lipid levels and migraine as well as migraine specifics (9, 13–15). In a population-based study from the Netherlands of men and women aged 20–65 years, increased total cholesterol and the total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio have been associated with migraine with aura (9). In a clinic-based study from Austria, patients with migraine had increased levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and oxidized LDL-C when compared to controls (13).

As the vast majority of previous studies evaluated the association between lipid levels and migraine among young or middle-aged patients, uncertainties remain about whether this association can be found in the elderly in whom risk of vascular disease is substantially increased compared with younger individuals.

Thus, we aimed to evaluate the relationship between lipid levels and history of overall and specific headache forms in the population-based Epidemiology of Vascular Aging (EVA) study and specifically hypothesized associations between increased lipid levels and migraine with aura among elderly individuals.

Methods

Study participants

Cross-sectional study among participants in the EVA study, a longitudinal study of cognitive and vascular aging that recruited men and women born between 1922 and 1932 from the electoral rolls of the city of Nantes, France (16). During the baseline visit (1991–1993), a total of 1,389 participants were enrolled. Standardized questionnaires were administered to ascertain information about demographics, occupation, medical history, and personal characteristics. Written informed consent was obtained from all participants and the study was approved by the Ethics Committee of the Hôpital de Kremlin-Bicêtre.

Migraine assessment

Information on migraine was ascertained during the second follow-up visit in a two-step approach and involved the 1188 participants who were still in active follow-up. First, during a face-to-face interview by trained personal, participants were asked standardized questions about life-time history of severe headaches and headache features. Second, participants who reported a life-time history of severe headache were asked to participate in a telephone interview with a neurologist specialized in headaches using a structured questionnaire with high reproducibility (17). Interviews were solely focused on headache and the neurologist was blinded to clinical, laboratory, and imaging data. Two hundred forty-two participants reported a history of severe headache on the questionnaire and were eligible for the interview. Of those, 4 died before the time of the interview, 4 were not reachable or opted not to participate, and 1 had severe hearing impairment, leaving 233 participants with a history of severe headache who were interviewed by a headache specialist. Information on detailed life-time history of headache, specific migraine features, and aura symptoms were ascertained during the interview.

Diagnosis of migraine and migraine subtypes was based on the second International Classification of Headache Disorders (ICHD II).(18) We a priori classified participants in the classes ‘no history of severe headache,’ ‘any history of severe headache.’ We distinguished ‘migraine’ and non-migraine’ headache by applying the ICHD II criteria for ‘probable migraine’ (fulfillment of all but one criteria for migraine without aura), which is used in many population-based studies to define migraine headache (4, 19). In addition, we classified patients with migraine according to migraine aura status.

Lipid level measurements

Blood samples were drawn between 8 and 9 AM after a 12-hour fast. Total cholesterol and triglyceride assays were performed by using the PAP enzymatic cholesterol kit (Reference 61227) and the PAP enzymatic triglyceride kit (Reference 759350), respectively, supplied by Biomérieux. HDL cholesterol was measured enzymatically after precipitation of apo B-containing lipoproteins with phosphotungstic acid and Mg²⁺ (precipitant Reference 543004, Boehringer). LDL cholesterol was computed with the Friedewald formula. All determinations were made daily. Cholesterol ratio was calculated taking the ratio of total cholesterol to HDL cholesterol.

Statistical analysis

Of the 1179 participants with complete headache information, we excluded 24 due to missing lipid level measurements, leaving 1155 participants for this study.

We compared the means of continuous and frequency of categorical characteristics of participants according to their headache status. We used multinomial logistic regression models to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of the association between the various lipid level tertiles and headache status using participants who were in the lowest lipid level tertile and who did not report a history of severe headache as reference group. We ran age- and multivariable-adjusted models. The multivariable models controlled age (continuous), gender, smoking status (ever, never, past), ever cholesterol medication use, alcohol consumption (continuous), systolic blood pressure (continuous), diastolic blood pressure (continuous) and body mass index (continuous). Less than 45 people were missing information on systolic blood pressure, diastolic blood pressure and body mass index and were assigned to the mean values for the cohort. No information was missing on any other covariate.

All analyses were performed using SAS version 9.1 (SAS Inc, Cary, NC); P values were two-tailed and a $P < 0.05$ was considered statistically significant.

Results

Of the 1155 participants with complete headache information, 230 (19.9%) reported a history of severe headache. Of the 166 participants fulfilling the criteria of probable migraine, 23 (13.9%) reported aura symptoms. The association between personal characteristics with no history of severe headache, non-migraine headache, migraine without aura and migraine with aura is summarized in Table 1. Participants with migraine were more likely to be female, to never have smoked, and consume less alcohol on average than the no history of severe headache or non-migraine headache groups.

We observed strong associations between increasing tertiles of total cholesterol and migraine with aura. Compared to participants who were in the lowest tertile of total cholesterol, those with in the 2nd tertile and 3rd tertiles of total cholesterol had relative risks (95% CI) of 4.67 (0.99–21.97) and 5.97 (1.29–27.61) for experiencing migraine with aura versus no severe headache. We also found a strong association between elevated triglycerides and migraine with aura (OR (95% CI) for 3rd tertile: 4.42 (1.32–14.77).) Migraine with aura was not associated with increased levels of any other biomarkers. Additionally, we did not see significant associations between increased biomarker levels and any other headache group.

Discussion

In this large, population-based sample of elderly individuals from France, elevated levels of total cholesterol and triglycerides were associated with migraine with aura. Increased levels of other biomarkers were not associated with any headache categories. Our research findings confirm previous studies linking migraine with increased levels of cholesterol and extend these findings to triglycerides and demonstrate that this association is still apparent among the elderly and limited to patients with migraine with aura.

Comparison with other population-based studies

A case-control study among normal weighted individuals found that migraineurs had increased levels of cholesterol, LDL-C and oxidized LDL-C compared to non-migraineurs controls. Those in the highest quartile of oxidized LDL-C had 7.93 times the odds of experiencing migraine compared those in the lowest quartile of oxidized LDL-C. However, they did not see any differences in the levels of oxidized LDL-C among migraineurs with and without aura (13). This result is similar to the findings of another study that observed a modest increase in the risk of elevated total cholesterol among migraineurs overall but did not see a difference in risk between migraineurs with and without aura (11). In contrast, a large population-based cohort study conducted in the Netherlands found an increased odds of migraine overall and migraine with aura among those with elevated total cholesterol. This effect was stronger among females who experience migraine with aura than among males who experience migraine with aura (9). Most studies to date have been performed among young to middle-aged populations (9, 11, 13). One of the few studies among the elderly found that elevated total cholesterol was associated with migraine especially among males (15). However, this study was not able to stratify their results based on aura status.

Strengths and limitations

Our study has several strengths, including the large number of participants drawn independently of headache status from the general population, classification of headache

status via phone interview conducted by neurologists who were specialized in headache disorders, and the large amount of covariate information which allowed us to control for potential confounding factors.

Several limitations should be considered when evaluating our results. First, despite of the large study size, we had relatively small number of participants in the migraine with aura subgroup (n=23). However, despite this small number we found significant and a priori hypothesized associations with specific lipid levels only in this subgroup. Second, our study is cross-sectional, which does not allow us to evaluate the direction of association. However, the vast majority of participants with headache reported first onset in young age during which lipid levels are usually lower. Third, despite adjustment for a large number of potential confounders, residual and unmeasurable confounding is possible since our study is observational. Lastly, participants in the EVA study were all aged ≥ 65 and were healthier and of higher social status as compared to the average French population of the same age range (20), which may affect extrapolation of our data to other populations.

Potential biological mechanisms

Given the small number of studies that examine the association between migraine and cholesterol levels, the biological link between elevated cholesterol levels and migraine with aura remains unclear. Recent basic science findings suggest that a bolus of cholesterol crystals given to mice can trigger cortical spreading depression (21). As this is the very likely correlate of migraine aura, it is possible that increased cholesterol levels may trigger migraine with aura attacks in some susceptible individuals. However, our data only provides indirect evidence to support such a hypothesis.

Practical implications

Because of the consistent link in independent population-based studies, migraine with aura should be considered a marker for increased lipid levels and evaluation of patients should be considered. Because there is no evidence that lowering lipid levels positively affect migraine with aura, treatment decisions should be made with regard to vascular disease prevention.

Future research directions

Further targeted research is warranted to evaluate the role of increased lipid levels among migraineurs with aura to better understand potential biological mechanisms. In addition, further research is needed to determine if change in cholesterol levels modify the occurrence or frequency of migraine with aura.

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Table 1

Association between headache status and personal characteristics in the Epidemiology of Vascular Ageing Study (N=1155)

Variable	No history of severe headache (n=925)	Non-migraine headache (n=64)	Migraine without aura (n=143)	Migraine with aura (n=23)
Age, years (SD)	69.0 (3.0)	69.1 (3.0)	69.1 (3.0)	69.0 (2.9)
Female, %	54.3	50.0	86.0	78.3
Cholesterol, mmol/l	6.1 (1.0)	6.1 (0.8)	6.2 (1.0)	6.6 (0.9)
LDL cholesterol, mmol/l	3.8 (0.9)	3.8 (0.8)	3.9 (0.9)	4.1 (0.7)
HDL cholesterol, mmol/l	1.7 (0.5)	1.7 (0.5)	1.8 (0.5)	1.9 (0.5)
Non-HDL cholesterol, mmol/l	4.4 (0.9)	4.4 (0.9)	4.4 (1.0)	4.8 (0.9)
Cholesterol ratio	3.7 (1.0)	4.4 (4.3)	3.6 (1.0)	3.9 (1.1)
Triglycerides, mmol/l	1.3 (0.6)	1.4 (0.7)	1.2 (0.6)	1.6 (0.8)
Systolic blood pressure, mmHg	135.9 (20.5)	135.4 (20.9)	131.2 (21.2)	132.7 (19.7)
Diastolic blood pressure, mmHg	77.3 (12.4)	76.5 (11.9)	75.3 (13.0)	77.1 (14.6)
Body mass index, kg/m ²	25.9 (3.8)	25.8 (3.9)	25.7 (4.2)	25.2 (3.6)
Smoking status, %				
Never	56.7	54.7	74.1	60.9
Past	34.6	34.4	21.7	30.4
Current	8.8	10.9	4.2	8.7
Alcohol intake, g/day	15.7 (18.0)	15.8 (20.7)	8.0 (11.7)	9.2 (13.8)
Ever used cholesterol medication, %	31.9	32.8	29.4	34.8

LDL=low density lipoprotein; HDL=high density lipoprotein; cholesterol ratio=total cholesterol/HDL cholesterol

Numbers are means (standard deviation) unless otherwise indicated.

Percentage may not add up to 100% due to rounding or missing values

Table 2

Multivariable-adjusted* relative risks headache status according to biomarker tertiles in the EVA Study (N=1155).

	No severe headache (n=925)			Non-migraine headache (n=64)			Migraine without aura (n=143)			Migraine with aura (n=23)		
	n	%	RR (95% CI)	n	%	RR (95% CI)	n	%	RR (95% CI)	n	%	RR (95% CI)
Total Cholesterol												
1 st tertile	318	34.4	1.00	21	32.8	1.00	44	30.8	1.00	2	8.7	1.00
2 nd tertile	309	33.4	1.37 (0.75, 2.50)	27	42.2	1.37 (0.75, 2.50)	45	31.5	0.94 (0.59, 1.49)	9	39.1	4.67 (0.99, 21.97)
3 rd tertile	298	32.2	0.86 (0.43, 1.72)	16	25.0	0.86 (0.43, 1.72)	54	37.8	0.97 (0.62, 1.52)	12	52.2	5.97 (1.29, 27.61)
LDL												
1 st tertile	310	33.5	1.00	23	35.9	1.00	46	32.2	1.00	5	21.7	1.00
2 nd tertile	316	34.2	0.97 (0.53, 1.78)	22	34.4	0.97 (0.53, 1.78)	47	32.9	0.98 (0.62, 1.54)	9	39.1	1.82 (0.60, 5.55)
3 rd tertile	299	32.3	0.89 (0.47, 1.69)	19	29.7	0.89 (0.47, 1.69)	50	35.0	0.95 (0.60, 1.49)	9	39.1	1.87 (0.61, 5.77)
HDL												
1 st tertile	326	35.2	1.00	21	32.8	1.00	35	24.5	1.00	6	26.1	1.00
2 nd tertile	306	33.1	1.34 (0.72, 2.50)	25	39.1	1.34 (0.72, 2.50)	54	37.8	1.22 (0.75, 1.96)	7	30.4	0.98 (0.32, 3.06)
3 rd tertile	293	31.7	1.02 (0.50, 2.09)	18	28.1	1.02 (0.50, 2.09)	54	37.8	1.14 (0.69, 1.88)	10	43.5	1.35 (0.44, 4.19)
Non-HDL												
1 st tertile	304	32.9	1.00	22	34.4	1.00	53	37.1	1.00	4	17.4	1.00
2 nd tertile	315	34.1	0.99 (0.53, 1.84)	22	34.4	0.99 (0.53, 1.84)	45	31.5	0.83 (0.53, 1.30)	10	43.5	2.66 (0.81, 8.75)
3 rd tertile	306	33.1	0.94 (0.50, 1.79)	20	31.3	0.94 (0.50, 1.79)	45	31.5	0.74 (0.47, 1.16)	9	39.1	2.39 (0.71, 8.05)
Triglycerides												
1 st tertile	308	33.3	1.00	20	31.3	1.00	55	38.5	1.00	4	17.4	1.00
2 nd tertile	317	34.3	0.90 (0.46, 1.73)	18	28.1	0.90 (0.46, 1.73)	47	32.9	0.85 (0.55, 1.31)	7	30.4	1.85 (0.53, 6.45)
3 rd tertile	300	32.4	1.43 (0.75, 2.72)	26	40.6	1.43 (0.75, 2.72)	41	28.7	0.88 (0.55, 1.41)	12	52.2	4.42 (1.32, 14.77)
Cholesterol Ratio												
1 st tertile	293	31.7	1.00	23	35.9	1.00	59	41.3	1.00	6	26.1	1.00
2 nd tertile	321	34.7	0.82 (0.44, 1.52)	21	32.8	0.82 (0.44, 1.52)	43	30.1	0.73 (0.47, 1.13)	8	34.8	1.45 (0.49, 4.32)
3 rd tertile	311	33.6	0.78 (0.41, 1.51)	20	31.3	0.78 (0.41, 1.51)	41	28.7	0.82 (0.51, 1.30)	9	39.1	2.03 (0.67, 6.20)

LDL=low density lipoprotein; HDL=high density lipoprotein; cholesterol ratio=total cholesterol/HDL cholesterol

Relative risks are odds ratios calculated from a multinomial logistic regression model using participants in the lowest tertile of each biomarker and without history of migraine as reference group.

* Adjusted for age, gender, smoking status, ever cholesterol medication use, alcohol consumption, systolic blood pressure, diastolic blood pressure and body mass index.

Tertile cutpoints for the first and second tertiles were defined as the following: total cholesterol: 5.71 and 6.49 mmol/L, LDL cholesterol: 3.42 and 4.19 mmol/L, HDL cholesterol 1.5 and 1.9 mmol/L, non-HDL cholesterol: 3.97 and 4.79 mmol/L, triglycerides: 0.98 and 1.42 mmol/L, and cholesterol ratio: 3.18 and 4.03 respectively. All values greater than these cutpoints were categorized as being in the third tertile.