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Authors

Lioutas, Vasileios-Arsenios
Beiser, Alexa
Himali, Jayandra
et al.

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Lacunar infarcts and deep intracerebral hemorrhage differences: A nested case-control analysis in the Framingham Heart Study

Vasileios-Arsenios Lioutas, MD[1,5], **Alexa Beiser, PhD**[2,3,5], **Jayandra Himali, PhD**[2,3,5], **Hugo Aparicio, MD**[3,5], **Jose Rafael Romero, MD**[3,5], **Charles DeCarli, MD**[4], and **Sudha Seshadri, MD**[3,5]

[1]Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA, USA

[2]Deparmtnet of Biostatistics, Boston University School of Public Health, Boston, MA, USA

[3]Department of Neurology, Boston University School of Medicine, Boston, MA, USA

[4]Department of Neurology, University of California Davis, Davis, CA, USA

[5]Framingham Heart Study

Abstract

Background and Purpose—Lacunar ischemic stroke (LS) and intracerebral hemorrhage (iCH) are two diverse manifestations of Small Vessel Disease (SVD). What predisposes some patients to ischemic stroke and others to hemorrhage is not well understood.

Methods—We performed a nested case-control study within the Framingham Heart Study comparing persons with incident iCH and LIS, to age- and sex-matched controls for baseline prevalence and levels of cardiovascular risk factors.

Results—We identified 118 LS (mean age 74 years, 51% male) and 108 iCH (75 years, 46% male) events. Hypertension, diabetes, smoking and obesity were strongly associated with LS. Hypertension, but not diabetes, smoking, or cholesterol levels increased the odds of iCH. Contrary to LS, iCH cases had lower BMI than their controls (26 vs 27); BMI<20 was associated with 4-fold higher odds for iCH. In direct comparison, LS cases had higher BMI (28 vs 26) and obesity prevalence (OR 3.1); BMI<20 was associated with significantly lower odds of LS (OR 0.1).

Conclusions—LS and iCH share hypertension, but not DM as a common risk factor. iCH cases had lower BMI compared not only to LS but to their controls as well; this finding is unexplained and merits further exploration

Keywords

Lacunar stroke; intracerebral hemorrhage; Obesity; Body Mass Index

Correspondence to: V. Lioutas, Beth Israel Deaconess Medical Center, Department of Neurology, 330 Brookline Avenue, Boston, MA, USA, 02215, Fax: 617-632-8920, Tel: 617-632-8913, vlioutas@bidmc.harvard.edu.

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None

Introduction

Lacunar stroke (LS) and primary intracerebral hemorrhage (iCH) share many common epidemiologic and neuroanatomical characteristics and are regarded as opposite ends of the same underlying process, collectively known as small-vessel disease (SVD)[1]. Prior studies have suggested that LS patients are older and more likely to have diabetes and higher cholesterol levels[2]. Given the radically different therapeutic implications of LS and iCH, it is important to better understand which factors predispose persons with similar underlying pathology of cerebral SVD to either ischemia or hemorrhage. We addressed this question by comparing risk factor profiles in persons with incident LS or iCH to age- and sex-matched stroke-free controls within the Framingham Heart Study (FHS).

Patients and Methods

We created two nested case-control samples from the FHS Original cohort enrolled in 1948 and examined biennially, and the Offspring cohort enrolled in 1971 and reexamined every four years (~99% Caucasians). We included participants who experienced a first iCH or LS between enrollment and 2012, and attended a clinic examination within 10 years before the stroke. Each stroke case was matched on cohort, sex, and age (within 2 years) to three stroke-free controls.

Written informed consent was obtained from all participants. The Institutional Review Board of Boston University Medical Center approved the consent form and original study design.

Additional information regarding risk factor definitions and stroke case ascertainment, are provided in the online data supplement.

Statistical analyses

Summaries of categorical variables are reported as proportions and continuous variables as means and standard deviation. In the iCH (or LS) sample, we used multivariable conditional logistic regression models to investigate the association between demographic and clinical characteristics and risk of iCH (or LS), adjusted for age and time between the clinical assessment and stroke event (or matching date). In a sample of cases only (iCH+LS), we used multivariable logistic regression to examine associations between the risk factors and type of stroke. Statistical significance was set at a two-sided $\alpha \leq 0.05$. Analyses were conducted in SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

We identified 118 incident LS and 106 incident iCH cases (mean 2 years between clinic examination and stroke). The baseline demographic and clinical characteristics of our cohort are summarized in Table 1.

LS cases vs. controls

Higher blood pressure, hypertension, diabetes, smoking, higher BMI, were each associated with greater odds of LS; diabetes had the strongest association (OR=4.44,95% CI 2.30–8.57) (Table 1). Persons with BMI ≥ 30 were nearly twice as likely to have LS as those with BMI <30. (Table 2)

iCH cases vs controls

Blood pressure and hypertension but not diabetes was associated with greater odds of iCH (Table 1). Higher BMI was associated with lower odds of iCH. Persons with BMI<20 were nearly four times as likely to have iCH as those with BMI ≥20. (Table 2)

iCH vs LS cases

Persons with a history of diabetes were more than 2.5 times as likely to have LS compared to persons with iCH. Higher BMI was associated with greater odds of LS:Cases with BMI ≥ 30 were more than 3 times as likely to have LS; those with BMI <20 were only 1/10 as likely to have LS.

To explore whether the relationship between lower BMI and iCH could be explained by development of dementia, we performed a separate analysis of BMI and iCH risk adjusting for cognitive impairment at the time of BMI measurement which yielded an OR of 5.0 (p=0.07).

Discussion

In this nested case-control study comparing individuals with incident LS and iCH separately with controls and with each other, we found that hypertension was strongly associated with both LS and iCH. Those with diabetes and those who were overweight or obese were significantly more likely to have LS, compared to either controls or persons with iCH. BMI<20 was associated with iCH compared not only for LS but to their controls as well.

Our findings underscore that hypertension is a significant risk factor for both LS and iCH[3,4], but demonstrate a more nuanced relationship between diabetes and SVD-related stroke. It is possible that the micro- and macrovascular effects of diabetes constitute a critical mediator that, in the presence of hypertension, predisposes to a thrombogenic process. This finding is in accordance with prior studies[2], but contradicts a recent study comparing iCH and LS cases where no difference in the prevalence of diabetes was found[5].

Of particular interest are the differences in risks associated with BMI wherein obesity predisposed to LS and low BMI predisposed to iCH. Prior studies examining the role of obesity in ICH risk have been conflicting: Some researchers have suggested that obesity is linked to iCH[6], its effect mediated by hypertension and diabetes; others have shown that BMI extremes (<18.5 and >30)[7] are associated with deep ICH risk and some suggest that underweight predisposes to lobar, but not deep ICH[8]. Although our sample size was small for such an analysis, we explored whether the association between lower BMI and iCH could be explained by the development of dementia, but our adjusted analysis yielded results

in the same direction (OR of 5.0 vs 3.8 in the analysis presented in Table 2) suggesting that this finding unlikely to be driven by cognitive impairment.

We hypothesize that the adipose tissue might play an important role in shifting the cerebral SVD manifestations towards either ischemia or haemorrhage. In a group that is well-balanced and homogeneous in terms of age, sex and race, as our cohort, BMI can be considered a crude surrogate marker of body fat[9]. An inverse association between total cholesterol and especially LDL and ICH risk has been consistently described[4,10] and the association between BMI and LDL levels has been found to be linear[11]. The adipose tissue is a complex organ, secreting several hormones that have cardiovascular effects[12]. Although very little is known about their relationship with the spectrum of cerebral SVD and especially ICH, it is possible that the cerebrovascular effects of certain adipokines are key in explaining our findings.

The stroke type ascertainment for lacunar strokes was based on clinical symptoms only before 1978–1980 and a combination of clinical presentation and imaging after 1980, when neuroimaging became more ubiquitous. However, only 23 (19.5%) of our LS cases occurred before 1980 and their risk factor profile was not different compared to those happening after 1980. The accuracy of etiologic classification of clinical lacunar syndrome in similar population studies is 75% [13]. Therefore it is unlikely that the lack of neuroimaging in the early stages of the FHS has affected the overall accuracy of LS cases classification.

Our study has limitations: the lipid panel measurements were not fasting which did not allow reliable measurements of triglycerides and LDL. Our assumptions regarding obesity were based solely on BMI measurements, as we did not have data on other obesity-related metrics such as waist-to-hip ratio available for all cases. The studied population is almost exclusively of European descent, limiting the generalizability to more racially diverse populations.

Conclusion

LS and ICH share hypertension, but not diabetes as a common risk factor. Lower BMI predisposed to iCH compared not only to persons with LS but to stroke-free controls as well. This finding is unexplained and a potential role of the adipose tissue and adipokines in modulating hemorrhage risk merits further exploration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Basic cohort characteristics and associations with LIS and ICH

	LIS				ICH				LIS vs ICH cases	
	cases	**controls**			**cases**	**Controls**				
	118	354			106	318				
Age at matching (years)	74±10	74±10			75±13	75±13				
Sex (% male)	51%				46%					
			OR [95%CI] *	p value			OR [95%CI] *	p value	OR [95%CI] *	p value
High School Graduate	62%	71%	0.69 [0.43–1.12]	0.134	70%	71%	0.94 [0.56–1.58]	0.813	0.71 [0.40–1.28]	0.260
College Graduate	11%	19%	**0.50 [0.25–1.00]**	**0.049**	15%	14%	1.04 [0.54–2.00]	0.917	0.69 [0.30–1.56]	0.370
Systolic Blood Pressure †	153±24	140±22	**1.03 [1.02–1.04]**	**<0.001**	150±28	139±21	**1.02 [1.01–1.03]**	**<0.001**	1.01 [0.99–1.02]	0.378
Diastolic Blood Pressure †	81±12	76±11	**1.05 [1.03–1.07]**	**<0.001**	80±15	75±11	**1.03 [1.01–1.06]**	**0.002**	1.01 [0.99–1.03]	0.48
Hypertension	85%	62%	**3.67 [2.06–6.57]**	**<0.001**	78%	67%	**1.82 [1.03–3.22]**	**0.040**	1.75 [0.87–3.57]	0.119
Cardiovascular Disease	32%	24%	1.51 [0.94–2.42]	0.086	28%	23%	1.40 [0.83–2.36]	0.208	1.20 [0.67–2.13]	0.548
Diabetes Mellitus	33%	10%	**4.44 [2.30–8.57]**	**<0.001**	16%	14%	1.09 [0.52–2.30]	0.818	**2.62 [1.22–5.62]**	**0.014**
Atrial Fibrillation	6.8%	4.8%	1.44 [0.59–3.52]	0.421	8.5%	5.7%	1.58 [0.66–3.78]	0.300	0.78 [0.28–2.12]	0.620
Smoking	21%	10%	**2.52 [1.34–4.75]**	**0.004**	18%	12%	1.75 [0.86–3.55]	0.124	1.18 [0.58–2.41]	0.649
Total Cholesterol ≠	5.43±1.32	5.40±1.03	1.00 [0.99–1.01]	0.613	5.40±1.19	5.28±1.09	1.00 [1.00–1.01]	0.285	1.00 [0.99–1.01]	0.874
High Density Lipoprotein ≠	**1.14**±0.33	**1.29**±0.41	**0.97 [0.94–0.99]**	**0.009**	1.34±0.39	1.37±0.49	1.00 [0.97–1.02]	0.696	**0.96 [0.93–0.99]**	**0.013**
Anticoagulant use	2.1%	0.7%	3.84 [0.52–28.43]	0.188	5.3%	2.1%	2.84 [0.70–11.50]		0.35 [0.06–2.01]	0.239

*odds of LS

†in mm Hg

≠in mmol/lOR indicates Odds ratio; CI, confidence interval

OR adjusted for age and time between clinical assessment and stroke (or matching date, for controls)

Table 2

Associations between BMI and LS and iCH

	LS				ICH				LS vs ICH cases	
	Cases	**Controls**	**OR [95% CI] ***	**p value**	**Cases**	**Control**	**OR [95% CI] ***	**p value**	**OR [95% CI] ***	**p value**
BMI - mean	28	27	**1.06 [1.01–1.12]**	**0.020**	26	27	**0.92 [0.86–0.98]**	**0.009**	**1.15 [1.08–1.23]**	**<0.001**
BMI ≥30 v. <30	36%	23%	**1.87 [1.13–3.08]**	**0.014**	15%	22%	0.66 [0.35–1.26]	0.210	**3.10 [1.57–6.11]**	**0.001**
BMI ≥25 v. <25	75%	65 %	1.61 [0.93–2.77]	0.088	41%	43%	0.66 [0.39–1.10]	0.110	**2.27 [1.26–4.12]**	**0.007**
BMI<20 v. ≥20	1%	3%	0.29 [0.04–2.34]	0.245	8%	2%	**3.78 [1.19–11.99]**	**0.024**	**0.10 [0.01–0.84]**	**0.034**

*Odds of LS

OR indicates Odds ratio; CI, confidence interval

OR adjusted for age and time between clinical assessment and stroke (or matching date, for controls)