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Genetic Epidemiology of Intracerebral Hemorrhage

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Abstract

Background—We have previously reported that family history of ICH was associated with both lobar and non-lobar ICH. We sought to further examine this finding by analyzing differences by age and Apolipoprotein E genotype.

Methods—All cases of hemorrhagic stroke in the Greater Cincinnati area are identified through retrospective screening and a subset is invited to undergo a direct interview and genetic testing. Interviewed subjects are matched to two controls by age, race and gender. Conditional stepwise logistic regression modeling was used to determine if having a first-degree relative with an ICH (FHICH) was an independent risk factor for ICH.

Results—Between 5/97 and 12/02, we recruited 333 cases of ICH. FHICH was found to be an independent risk factor for both lobar ICH (OR=3.9; p=0.04) and non-lobar ICH (OR=5.4; p=0.01) after controlling for the presence of numerous variables. Among non-lobar ICH cases the risk appeared to be predominately in those <70 years of age. The presence of apolipoprotein E4 was associated with lobar ICH = 70 years of age but not < 70 years of age.

Conclusion—Family history of ICH appears to be a significant risk factor for non-lobar ICH <70 years of age. Presence of Apolipoprotein E4 appears to be a risk factor for lobar ICH = 70 years of age but not < 70 years of age. Family history of ICH is a risk factor for lobar ICH after controlling for the presence of Apo E4.

Subject Codes

Genetics; Stroke; Intracerebral Hemorrhage; Family History; Apolipoprotein E

Introduction

Spontaneous intracerebral hemorrhage (ICH) occurs with an annual incidence rate of 15–19 per 100,000.[1] The genetic epidemiology of ICH has had little attention and yet is critical to designing appropriate studies to examine the phenotype. We have previously reported that having a history of a first-degree relative with ICH (FHICH) is an independent risk factor for lobar and non-lobar ICH.[2] We also reported that family history of any stroke was a significant risk factor for ICH subjects <70 years compared to those >= 70 years.[3] The mechanisms of ICH vary by location and may vary by age.[2] To date, there have been no reports on family

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history of ICH or the impact of Apolipoprotein E alleles when divided by age and location of ICH. Identifying which group of subjects is most appropriate for study is critical to proper study design.

Differences in risk by age may be important for several reasons. Hypertension appears to be a greater risk factor at younger ages than older ages.[4] By contrast, cerebral amyloid angiopathy (CAA) is rarely found (<10%) in those <70 years. Apolipoprotein E alleles have been associated with CAA and lobar ICH and we have reported that 10–44% of lobar ICH cases are attributable to variation in Apo E alleles.[2] If Apo E alleles mediate the risk of lobar ICH through CAA, however, the risk from Apo E alleles should occur only among older patients (>70 years). We examined whether family history of ICH is a significant risk factor for both lobar and non-lobar ICH by age and location and included genotyping of Apolipoprotein E alleles.

Methods

Subjects

The methodology of this ongoing study has been previously published.[2, 5] All patients residing within 50 miles of the University of Cincinnati with a potential ICH or subarachnoid hemorrhage (SAH) are identified by surveillance of all 16 adult hospitals and through hospital discharge diagnoses (ICD-9: 430–438.9). Cases of ICH due to vascular malformations or aneurysm were excluded from the current analysis. Cases are eligible if >18 years old and cases secondary to trauma or brain tumor are excluded. Cases are excluded if contact was not made within 90 days of stroke since some subjects may not be able to accurately recall details beyond 90 days. This study was approved by the Institutional Review Board at all participating hospitals and informed consent was obtained from all subjects undergoing direct interview and genetic sampling.

The definition for ICH is adapted from the Classification of Cerebrovascular Disease III – 1989.[6] ICH is defined as nontraumatic abrupt onset of severe headache, altered level of consciousness, and/or focal neurologic deficit that is associated with a focal collection of blood within the brain parenchyma as observed on CT, MRI or at autopsy and is not due to hemorrhagic conversion of a cerebral infarction.

All cases underwent medical record abstraction. Cases were approached for direct interview as well as genetic testing. Those cases that consented to enroll into the interview arm were matched by age, race and gender to two population-based controls identified through random digit dialing.

Race/ethnicitiy and risk factors of diabetes, hypercholesterolemia, hypertension, current (within six months) and prior smoking, and frequent alcohol use were defined by history. Body mass index was calculated from the reported weight and height. Apolipoprotein E genotype was determined using standard polymerase chain reaction methods.[7] Lobar ICH was defined as an ICH occurring predominately in the cortical or subcortical white matter area. Nonlobar ICH was defined as an ICH arising predominately from the deep basal ganglia, brainstem or cerebellum.

For family history of stroke, subjects are asked: “To your knowledge, has any of the following members of your biologic family ever had any of the following illnesses/conditions?: ‘ischemic stroke’, ‘transient ischemic attack sometimes called mini-stroke’, ‘intracerebral hemorrhage’, ‘subarachnoid hemorrhage’, ‘Alzheimer’s disease’, ‘Dementia’, or a ‘brain aneurysm’?” The interviewer provides a brief explanation of each condition. The vast majority of subjects state that they do not know what type of stroke their relatives had. When someone answers positively for ICH, they are still asked if any could have had a subarachnoid hemorrhage or a brain

aneurysm. If they are unsure after querying these points, then they are recorded as 'unknown'. The interviewers are unaware of the hypotheses of the study and are trained specifically to avoid 'suggesting' diagnoses or associations.

Data Analyses

The data were managed and analyzed using SAS® version 8.2 (SAS Institute, Cary, NC). Association between each risk factor of interest and ICH was performed using a matched logistic regression approach utilizing PROC PHREG®. A prespecified age-cutoff of 70 years was chosen based on the increased prevalence of cerebral amyloid angiopathy after the age of 70[2, 8] and preliminary data which demonstrated that family history of stroke was more common for ICH cases <70 years.[3] All variables examined are listed in the tables and were pre-specified. All variables significant in bivariate analysis ($p<0.10$) were included in the initial model and then backward eliminated. Other risk factors were treated as covariates in examining the explanatory variables. Significance in the final model was defined as $p<0.05$.

Results

Between 5/97 and 12/02, 560 cases were enrolled in the direct medical interview, and genetic sampling arm; 119 were lobar ICH, 214 were non-lobar ICH and the remaining 227 were SAH. All analyses described below apply only to the 333 cases of ICH and their matched controls.

Table 1 provides the prevalence of risk factors and bivariate odds ratios (OR) for association with lobar ICH and for subgroups of < 70 years and =70 years. Table 2 demonstrates a multivariate analysis for the same risk factors. Tables 3 and 4 provide similar data for non-lobar ICH.

A positive history of ICH in first-degree relatives (FHICH) was a significant risk factor for both lobar and non-lobar ICH cases. Presence of Apo E4 was associated with lobar ICH =70 years but fell out of significance for lobar ICH <70 years and was not found to be associated with non-lobar ICH. FHICH was also associated with non-lobar ICH <70 years but not with non-lobar ICH =70 years of age. No significant difference was identified for lobar ICH after dividing by age.

Risk factors such as hypertension and Apo E alleles are known to aggregate within families. We examined the prevalence of risk factors between those that were positive for FHICH compared to those that were negative (data not shown). None of the examined factors occurred more often among those with a FHICH compared to cases without. Hypertension showed a trend towards association for FHICH among non-lobar ICH cases compared to controls (92% vs. 72%; p=0.13). Apo E4 was not present more often among lobar ICH with FHICH compared to those without (26% vs. 33% p=0.58).

When examining family history of a phenotype, artifactual enhancement may be a concern. Increased numbers of affected first-degree relatives may result from cases having larger family size or older average age compared to controls. After 2/1/01, 75 interviewed cases and 131 controls had additional questions asked regarding siblings and offspring. The average number of siblings was 3.1 for cases and 3.0 for controls (p=0.83) and the average number of offspring was 2.7 for cases and 2.2 for controls (p=0.05). There was no difference in the rate of ICH affecting offspring. When we compared the cases with a FHICH to the cases without, the average age was 66.6 years compared to 65.1 years (p=0.69). Thus, the FHICH among cases does not appear to be related to older average age of relatives or size of families.

Vascular malformations may lead to ICH and yet not be detected by CT scanning. We examined the rate of additional testing. Overall, 39% of subjects received an MRI (24%), cerebral

angiography (10%) or both (5%) tests. For those age less than 55, 77% of subjects received either an MRI (30%), cerebral angiography (30%) or both (17%).

Discussion

We report that having a FHICH is a risk factor for non-lobar ICH cases <70 years. This difference by age was not found among lobar ICH cases. The implications of these findings are that the search for susceptibility genes would be best focused upon non-lobar ICH <70 years and among lobar ICH cases.

The overall prevalence of FHICH was small in cases and controls. Combined with the high mortality rate of ICH, this suggests that the ability to recruit large numbers of living sibling or affected relative pairs is limited. In addition, the variation in risk factors between lobar and non-lobar ICH cases suggest that identifying the location of ICH among relatives will also be important. We conclude that studies on the genetic epidemiology of ICH should be centered on association studies rather than family studies.

While the familial clustering of stroke is not a novel finding, few studies have examined whether the stroke subtype of ICH aggregates within families and none examined the importance of location or age. Alberts et. al. and Graffagnino et. al. reported on family history of ICH in a single institution study.[9, 10] Neither study controlled for the presence of Apo E alleles. Although the number of cases with a FHICH in our study is small, the differences were statistically significant. In addition, we report a more conservative figure of the rate of family history of ICH than currently reported in the literature (9.8% by Alberts et al and 15% by Graffagnino et al.).[9, 10]

Hypertension, high cholesterol, anti-coagulant use, education level and frequent alcohol use have been previously associated with ICH.[2, 11, 12] Anticoagulant use appeared to be a factor for lobar ICH and for non-lobar ICH greater than 70 years of age. Some studies have suggested that anticoagulant use may interact with Apo E alleles to increase the risk of lobar ICH.[13]

Apo E4 was associated with lobar ICH =70 years but not <70 years. These findings support the role of Apo E4 in cerebral amyloid angiopathy, which rarely occurs in persons <70 years.[2, 8] Despite controlling for the presence of Apo E4, FHICH was still significant, suggesting that other familial factors may be present.

One possible explanation for familial aggregation of ICH is that risk factors for ICH, such as hypertension, may aggregate within families. Yet we did not find any risk factor that occurred more often among those with FHICH compared to without. Thus, the increased prevalence of FHICH does not appear to be associated with the familial aggregation of risk factors.

Conclusions

Family history of ICH appears to be a significant risk factor for non-lobar ICH <70 years. Apolipoprotein E4 is a risk factor for lobar ICH = 70 years but not < 70 years. Family history of ICH is a risk factor for lobar ICH despite controlling for the presence of Apo E4.

References

1. Broderick J, Miller R, Khoury J, et al. Incidence Rates of Stroke for Blacks and Whites: Preliminary Results from the Greater Cincinnati/Northern Kentucky Stroke Study. Stroke 2001;32:320.
2. Woo D, Sauerbeck LR, Kissela BM, et al. Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study. Stroke 2002;33:1190–6. [PubMed: 11988589]discussion 1196.

3. Woo D, Sauerbeck L, Khoury J, et al. Familial aggregation of stroke and intracerebral hemorrhage. Stroke 2000;31:316.
4. Flaherty ML, Woo D, Haverbusch M, et al. Incidence rates and temporal trends of intracerebral hemorrhage defined by location: A population-based study. Abstract Neurology 2004;62:A101–102.
5. Kissela BM, Sauerbeck L, Woo D, et al. Subarachnoid hemorrhage: a preventable disease with a heritable component. Stroke 2002;33:1321–6. [PubMed: 11988610]
6. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators [see comments]. New England Journal of Medicine 1990;323:1505–11. [PubMed: 2233931]
7. Rebeck GW, Reiter JS, Strickland DK, Hyman BT. Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptor interactions. Neuron 1993;11:575–80. [PubMed: 8398148]
8. Greenberg SM, Briggs ME, Hyman BT, et al. Apolipoprotein E epsilon 4 is associated with the presence and earlier onset of hemorrhage in cerebral amyloid angiopathy. Stroke; a Journal of Cerebral Circulation 1996;27:1333–7. [PubMed: 8711797]
9. Alberts MJ, McCarron MO, Hoffmann KL, Graffagnino C. Familial clustering of intracerebral hemorrhage: a prospective study in North Carolina. Neuroepidemiology 2002;21:18–21. [PubMed: 11744821]
10. Graffagnino C, Herbstreith MH, Roses AD, Alberts MJ. A molecular genetic study of intracerebral hemorrhage. Arch Neurol 1994;51:981–4. [PubMed: 7945009]
11. Woo D, Haverbusch M, Sekar P, et al. Effect of untreated hypertension on hemorrhagic stroke. Stroke 2004;35:1703–8. [PubMed: 15155969]
12. Woo D, Kissela BM, Khoury JC, et al. Hypercholesterolemia, HMG-CoA reductase inhibitors, and risk of intracerebral hemorrhage: a case-control study. Stroke 2004;35:1360–4. [PubMed: 15087556]
13. Rosand J, Hylek EM, O'Donnell HC, Greenberg SM. Warfarin-associated hemorrhage and cerebral amyloid angiopathy: a genetic and pathologic study. Neurology 2000;55:947–51. [PubMed: 11061249]

Table 1

Prevalence and Bivariate Risk Factors for Lobar ICH All Ages, = 70 years and < 70 years

Risk Factor	Lobar ICH (N=119)			Lobar ICH = 70 years (N=61)			Lobar ICH <70 years (N=58)		
	Case n(%)	Control n(%)	Odds ratio (95% CI)	Case n(%)	Control n(%)	Odds ratio (95% CI)	Case n(%)	Control n(%)	Odds ratio (95% CI)
ICH 1st Degree relative	7(5.9)	5(2.2)	3.0(0.9–10.4)	4(6.6)	3(2.5)	3.3(0.6–18.9)	3(5.2)	2(1.8)	2.6(0.4–16.0)
Hypertension	55(46.2)	111(48.5)	0.9(0.6–1.4)	32(52.5)	68(57.6)	0.8(0.4–1.5)	23(39.7)	43(38.7)	1.0(0.5–2.0)
High	36(30.3)	86(37.6)	0.7(0.5–1.2)	21(34.4)	47(39.8)	0.8(0.4–1.5)	15(25.9)	39(35.1)	0.6(0.3–1.3)
Current Smoking	32(26.9)	46(20.1)	1.4(0.8–2.5)	8(13.1)	14(11.9)	1.1(0.4–2.9)	24(41.4)	32(28.8)	1.6(0.7–3.3)
Former Smoking	39(32.8)	89(38.9)	0.8(0.5–1.4)	26(42.6)	53(44.9)	0.9(0.5–1.8)	13(22.4)	36(32.4)	0.7(0.3–1.6)
Frequent Alcohol	10(8.4)	7(3.1)	2.8(1.0–7.7)	5(8.2)	3(2.5)	3.9(0.7–20.9)	5(8.6)	4(3.6)	2.2(0.6–8.1)
BMI:Mean(SD)	26.5(6.1)	27.6(5.8)	0.96(0.92–1.01)	24.5(4.4)	26.7(5.1)	0.90(0.84–0.97)	28.6(7.0)	28.6(6.4)	1.00(0.95–1.06)
Anti–Coagulant Use	16(13.5)	7(3.1)	5.7(2.1–15.6)	11(18.0)	4(3.4)	6.6(1.8–23.8)	5(8.6)	3(2.7)	4.3(0.8–22.8)
Less than High School Education	30(25.2)	33(14.4)	2.4(1.3–4.6)	24(39.3)	20(17.0)	4.9(2.0–11.8)	6(10.3)	13(11.7)	0.9(0.3–2.6)
High School	47(39.5)	85(37.1)	1.5(0.9–2.4)	22(36.1)	41(34.8)	2.4(1.0–5.6)	25(43.1)	44(39.6)	1.1(0.6–2.2)
Apo E2	29(24.4)	35(15.3)	1.5(0.7–3.6)	16(26.2)	16(13.6)	3.6(0.9–14.5)	13(22.4)	19(17.1)	0.8(0.3–2.7)
Apo E4	46(38.7)	58(25.3)	1.9(1.2–3.0)	28(45.9)	29(24.6)	2.6(1.3–5.1)	18(31.0)	29(26.1)	1.3(0.7–2.6)

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Table 2

Multivariate Risk Factors for Lobar ICH, Lobar ICH =70 Years of Age and Lobar ICH <70 Years.

Risk Factor	Lobar ICH		Lobar ICH =70 years		Lobar ICH <70 Years	
	Multivariate Odds ratio (95% CI)	p-value	Multivariate Odds ratio (95% CI)	p-value	Multivariate Odds ratio (95% CI)	p-value
ICH 1st Degree relative	3.9(1.1–14.4)	0.0384	4.8(0.6–38.0)	0.1352	3.0(0.5–19.6)	0.2556
Frequent Alcohol	3.9(1.2–12.6)	0.0226	8.6(1.2–64.0)	0.0350	N.S.	N.S.
BMI:Mean(SD)	N.S.	N.S.	0.91(0.82–1.00)	0.0543	N.S.	N.S.
Anti-Coagulant Use	5.7(1.9–16.7)	0.0015	6.0(1.2–29.7)	0.0282	4.7(0.9–25.9)	0.0749
Less than High School Education	2.5(1.3–4.8)	0.0090	6.6(2.2–19.8)	0.0007	N.S.	N.S.
High School Education	1.4(0.9–2.4)	0.1736	2.4(0.9–6.5)	0.0872	N.S.	N.S.
Apo E4	2.1(1.3–3.6)	0.0050	3.5(1.4–8.8)	0.0065	N.S.	N.S.

Table 3

Prevalence and Bivariate Risk Factors for Non-Lobar ICH All Ages, = 70 years and < 70 years

Risk Factor	Non-Lobar ICH (n=214)			Non-Lobar ICH = 70 years (N=92)			Non-Lobar ICH <70 years (n=122)		
	Case n(%)	Control n(%)	Odds ratio (95% CI)	Case n(%)	Control n(%)	Odds ratio (95% CI)	Case n(%)	Control n(%)	Odds ratio (95% CI)
ICH 1st Degree relative	12(5.6)	5(1.2)	5.7(1.8–17.6)	5(5.4)	3(1.8)	4.3(0.8–22.8)	7(5.7)	2(0.9)	7.0(1.5–33.7)
Hypertension	156(72.9)	189(46.7)	3.5(2.4–5.3)	67(72.8)	88(51.5)	2.7(1.5–4.9)	89(73.0)	101(43.2)	4.3(2.5–7.5)
High Cholesterol	64(29.9)	171(42.2)	0.6(0.4–0.8)	29(31.5)	81(47.4)	0.5(0.3–0.9)	35(28.7)	90(38.5)	0.6(0.4–1.0)
Current Smoking	52(24.3)	89(22.0)	1.1(0.7–1.8)	9(9.8)	20(11.7)	0.8(0.3–1.9)	43(35.3)	69(29.5)	1.3(0.7–2.2)
Former Smoking	74(34.6)	155(38.3)	0.9(0.6–1.3)	37(40.2)	73(42.7)	0.9(0.5–1.5)	37(30.3)	82(35.0)	0.9(0.5–1.6)
Frequent Alcohol	18(8.4)	28(6.9)	1.3(0.7–2.4)	3(3.3)	5(2.9)	1.2(0.3–5.0)	15(12.3)	23(9.8)	1.3(0.6–2.7)
BMI:Mean(SD)	27.6(7.6)	28.2(6.0)	0.99(0.96–1.02)	24.7(4.8)	27.4(5.1)	0.88(0.83–0.94)	29.9(8.6)	28.8(6.5)	1.02(0.99–1.06)
Anti-Coagulant Use	28(13.1)	19(4.7)	3.3(1.8–6.3)	17(18.5)	12(7.0)	3.5(1.5–8.2)	11(9.0)	7(3.0)	3.1(1.2–8.1)
Less than High School Education	57(26.6)	54(13.3)	3.6(2.2–5.9)	28(30.4)	31(18.1)	3.6(1.7–7.7)	29(23.8)	23(9.8)	3.9(2.0–7.8)
High School Education	84(39.3)	133(32.8)	2.2(1.4–3.4)	39(42.4)	59(34.5)	2.7(1.3–5.5)	45(36.9)	74(31.6)	1.9(1.1–3.3)
Apo E2	38(17.8)	68(16.8)	1.9(0.8–4.7)	14(15.2)	25(14.6)	1.3(0.2–8.0)	24(19.7)	43(18.4)	2.1(0.7–6.2)
Apo E4	61(28.5)	105(25.9)	1.1(0.8–1.6)	24(26.1)	38(22.2)	1.3(0.7–2.4)	37(30.3)	67(28.6)	1.0(0.7–1.7)

Table 4

Multivariate Risk Factors for Non-Lobar ICH, Non-Lobar ICH =70 Years of Age and Non-Lobar ICH <70 Years

Risk Factor	Non-Lobar ICH Multivariate Odds ratio (95% CI)	p-value	Non-Lobar ICH =70 years Multivariate Odds ratio (95% CI)	p-value	Non-Lobar ICH <70 Years Multivariate Odds ratio (95% CI)	p-value
ICH 1st Degree relative	5.4(1.5–19.5)	0.0098	1.7(0.2–11.7)	0.6064	6.2(1.0–38.1)	0.0473
Hypertension	3.2(2.1–5.0)	<0.0001	3.5(1.7–7.4)	0.0009	3.9(2.2–7.0)	<0.0001
High Cholesterol	0.5(0.3–0.8)	0.0008	0.4(0.2–0.7)	0.0036	0.6(0.4–1.0)	0.0580
BMI:Mean(SD)	N.S.	N.S.	0.86(0.80–0.93)	0.0002	N.S.	N.S.
Anti-Coagulant Use	2.5(1.3–5.0)	0.0076	4.2(1.5–11.8)	0.0070	N.S.	N.S.
Less than High School Education	3.4(2.0–5.8)	<0.0001	5.2(2.1–13.1)	0.0005	2.8(1.4–5.9)	0.0052
High School Education	2.1(1.3–3.4)	0.0016	3.0(1.2–7.3)	0.0174	1.7(0.9–2.9)	0.0809