Original Paper

Neuro
epidemiology

Neuroepidemiology 2010;34:214–221
DOI: 10.1159/000289353

Received: October 5, 2009
Accepted: January 8, 2010
Published online: March 3, 2010

Incidence of Lobar and Non-Lobar Spontaneous Intracerebral Haemorrhage in a Predominantly Hispanic-Mestizo Population – The PISCIS Stroke Project: A Community-Based Prospective Study in Iquique, Chile

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Key Words

Cerebrovascular disease · Incidence · Intracerebral haemorrhage · Risk factors · Chile · Stroke · Hispanic population

Abstract

Background: The incidence of intracerebral haemorrhage (ICH) in Hispanics is high, especially of non-lobar ICH. Our aim was to ascertain prospectively the incidence of first-ever spontaneous ICH (SICH) stratified by localisation in a Hispanic-Mestizo population of the north of Chile. ***Methods:*** Between July 2000 and June 2002 all possible cases of ICH were ascertained from multiple overlapping sources. The cases were allocated according to localisation. Those with vascular malformations or non-identifiable localisations were excluded. ***Results:*** We identified a total of 69 cases of first-ever ICH. Of these, 64 (92.7%) had SICH, of which we allocated 58 cases (84%) to non-lobar or lobar localisation. The mean age was 57.3 ± 17 years, and 62.3% of the subjects were male. The age-adjusted incidence rates were 13.8 (non-lobar) and 4.9 (lobar) per 100,000 person-years. Non-lobar SICH was more frequent in young males and lobar SICH in older women. The non-lobar-to-lobar ratio was similar to previous findings in Hispanics. Hypertension was more frequent in non-lobar SICH and in diabetes, heavy drinking and antithrombotic use in lobar SICH, but in none significantly. There was no association between localisation and prognosis. ***Conclusions:*** The incidence of non-lobar SICH was high, but lower than in most non-white populations. This lower incidence could be due to a lower population prevalence of risk factors, a higher socioeconomic level in this population, or chance.

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Introduction

The proportion and incidence of intracerebral haemorrhage (ICH) in non-white communities has usually been found to be higher than that of whites [1]. The same has been reported for medium-to-low-income countries compared to high-income countries [2, 3]. Populations of Hispanic ethnic background living in the USA have been shown to have a higher incidence of ICH than non-Hispanic whites, both in community studies and hospital series [4–6].

The higher proportion and incidence of ICH in Hispanics has been attributed to a higher prevalence of untreated hypertension, diabetes, alcohol abuse, other risks associated with race/ethnicity, and socioeconomic factors [7–11]. It has been proposed that non-white communities are at a higher risk of non-lobar hypertension-related ICH as opposed to lobar haemorrhages, which are associated with vascular malformations in the young and with amyloid angiopathy in the elderly [8, 11–13].

It has previously been shown that the epidemiology of stroke and prevalence of risk factors is different in migrant and non-migrant populations [14]. All previous studies of the incidence of ICH by site of bleeding have been performed in Hispanic immigrants to the USA. It is unknown if these findings are similar in non-immigrant Hispanic populations living in Latin American countries. Previous community studies in Latin America have not reported on the incidence of ICH by localisation [15–19].

The purpose of this study was to report the incidence of spontaneous ICH (SICH) by localisation in a South American, predominantly Hispanic-Mestizo community and to compare our results with those on other populations. Our hypothesis was that the incidence rate of non-lobar SICH would be comparable to other Hispanic communities; higher than in whites, but lower than that reported in Asian and black populations.

Methods

The PISCIS (Proyecto de Investigación de Stroke en Chile: Iquique Stroke Study) is a community-based incidence study in a Hispanic-Mestizo population previously described in detail [15]. Iquique has 200,000 inhabitants, and is a geographically isolated port in the Atacama Desert. We ascertained patients with symptoms suggesting a stroke or transient ischaemic attack from July 1, 2000, to June 30, 2002. We made a special effort to identify all strokes unbiased by hospital admission or outpatient referral and to obtain brain computed tomography (CT) scans or a necropsy as soon as possible. We prospectively checked multiple overlapping sources of cases including emergency department, hospital admission and discharge lists of the three hospitals. Medical wards, intensive care units and beds in neurosurgery departments were checked weekly (hot pursuit). CT scan order forms were screened monthly, as well as nursing homes, outpatient clinics and death certificates (cold pursuit). We held regular meetings with physicians working in the city, encouraging them to refer patients suspected of having a stroke, and informed the public via a campaign in the media. One of the field investigators (L.P. or A.E.) examined all patients identified as soon as possible after symptom onset and arranged for a CT scan to be promptly performed. A digital subtraction angiography (DSA) was performed whenever possible or clinically necessary. DSA was usually performed in ICH patients if they were under 40 years of age or non-hypertensive and had lobar ICH. The radiological data were reviewed in all cases by a radiologist unblinded to the clinical data. We obtained information about cardiovascular risk factors from the patients, next of kin or chart review and defined them as previously described [15]. A trained nurse followed the cases the first and sixth month after symptom onset and performed a personal or telephonic interview with the patient and/or next of kin using a standardised questionnaire. She obtained a modified Rankin score. Clinical notes and death certificates were checked when appropriate.

Ethics

The ethical committee of the local health service in Iquique approved the protocol of this observational study. No tests beyond those of regular practice were performed. All patient data were analysed after anonymisation.

Allocation and ICH Type Classification by Localisation

The clinical data, laboratory exams and imaging (CT and DSA) results were sent to the allocation committee where 2 neurologists (P.M.L., C.S., G.A., F.A. and/or W.F.) allocated the patients according to their pathological type. We diagnosed ICH in patients with acute stroke in which a brain CT showed an area of high attenuation in a region compatible with the clinical signs and symptoms, or in which postmortem examination showed ICH. We excluded all cases with ICH resulting from non-vascular causes (tumour or trauma). Two different neurologists (P.M.L. and L.P.) rereviewed all ICH cases and allocated them by consensus to either SICH or secondary to vascular malformation (arteriovenous malformation, AVM, or a ruptured cerebral saccular aneurysm) and to 1 of 2 possible localisations: lobar or non-lobar. We defined as lobar any SICH in the supratentorial lobes, and as non-lobar any SICH in basal ganglia, thalami, the brainstem or cerebellum. Cases with intraventricular extension could be either lobar or non-lobar. The allocation according to localisation was blinded to risk factors except gender. We excluded patients with vascular malformations from the analysis to test our hypothesis in SICH only.

Statistical Methods

We adjusted the rates of annual first-ever SICH by localisation to the 2002 Chilean, Segi's European and world [20], and to the US 1990 [21] populations, using the direct method. We obtained the denominator from the 2002 national census. We calculated CI for crude and age-sex-specific rates assuming a Poisson distribution for counts of less than 100. We calculated CI for age-adjusted rates according to the Keyfitz formula [22]. We calculated non-lobar-to-lobar ratios in population-based studies and the 95% CI

assuming a binomial distribution according to Silcocks [23]. We compared proportions by the χ^2 or Fisher exact tests. The unpaired t test was used to compare mean ages. All tests were two tailed and $p < 0.05$ considered significant. The paper is reported following the STROBE statement [24].

Results

Seventy-seven cases had an ICH, of which 69 (89.6%) were first-ever in a lifetime. We identified 52 cases (75.4%) at the emergency room, 6 on the wards (8.7%), 5 (7.2%) in outpatient clinics, 3 (4.3%) from death certificates and 3 elsewhere. The median (IQR) time from symptom onset to CT scan was 1 (3) day(s) and 38 cases (72%) had a CT scan within 48 h of onset. In 17 cases (24.6%), a DSA was performed based on clinical suspicion of a vascular malformation. Four cases had an AVM. These were all normotensive males with lobar ICH and a mean age of 12.2 (7) years (range: 4–19 years). Their prognosis was very poor as half were scored 5 on the Rankin Scale and the rest was dead at 1 month. Another case was a 62-year-old hypertensive male with a ruptured cerebral aneurysm that bled into the ventricles, and he was dead at 30 days. We excluded these 5 cases from this analysis. In 6 other cases, it was not possible to fix the localisation of the SICH. Three had massive cortical/subcortical ICH, and of the other 3 we were unable to obtain the films. The mean age of these cases was 76 (9) years, and 3 of them were men. Their prognosis was poor; half died during the first month and only 2 (33.3%) were independent at 6 months. We also excluded them from this analysis.

We analysed 58 cases (fig. 1). The frequency distribution according to localisation was: 43 non-lobar (74.1%; 95% CI: 60.9–84.5%) and 15 lobar (25.9%; 95% CI: 15.2–34%). A total of 15 (25.9%; 95% CI: 15.2–34%) had intraventricular haemorrhage, of which 2 (13.3%) were lobar and 13 (86.6%) non-lobar cases. Ten (66.7%) of these cases were men and 7 (46.7%) were dead at 1 month. There were 5 cases (11.6%; 95% CI: 3.9–25.1%) of cerebellar or brainstem non-lobar SICH [4 men (80%); mean age: 51.6 (16.6) years], of which 3 (60%) were dead at 1 month, compared to only 19% in the deep basal ganglia ($p = 0.2$).

The crude incidence per year of first-ever SICH by localisation was: 10.8 non-lobar (95% CI: 7.8–14.6) and 3.8 lobar (95% CI: 2.1–6.2) cases per 100,000 person-years. The age-adjusted incidence rates per year based on the world population were: 13.8 non-lobar (95% CI: 11.7–15.9) and 4.9 lobar (95% CI: 3.6–6.2) cases per 100,000 person-years (table 1). The non-lobar-to-lobar age-adjusted rate ratio was 2.8 (95% CI: 1.4–5.1).

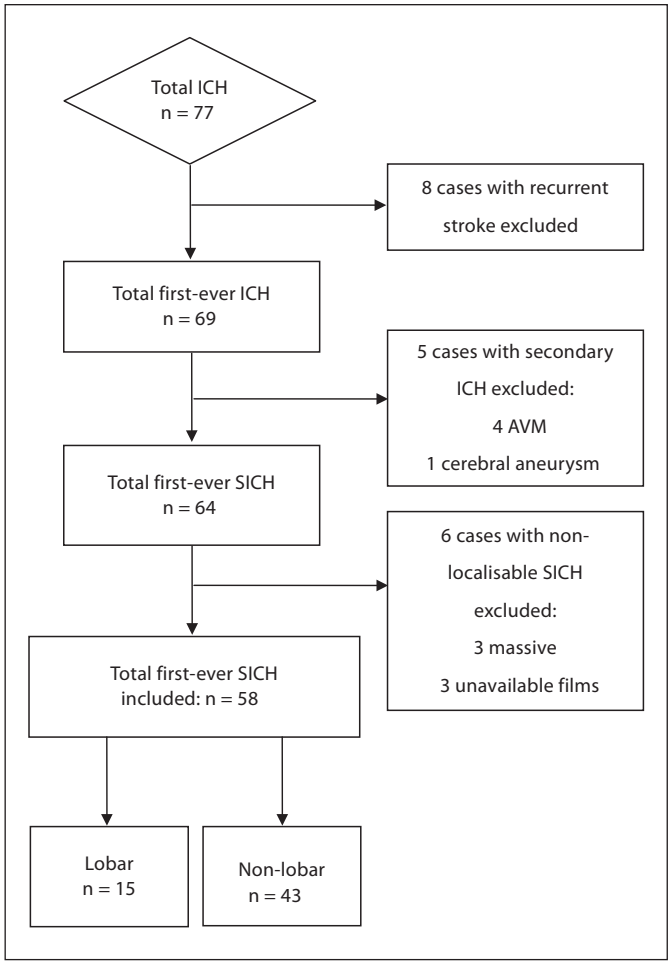

Fig. 1. Flow chart of patients with first-ever SICH included.

The incidence of both lobar and non-lobar SICH increased with age in both sexes (table 1). The overall male-to-female rate ratio was the same for lobar and non-lobar SICH: 1.6 (95% CI: 0.6–3.6) and 1.6 (95% CI: 0.8–2.8), respectively. Women had higher rates of lobar SICH in the older age groups, and males had increased rates in non-lobar SICH in the middle and younger age groups (table 2).

The distribution of cardiovascular risk factors by SICH localisation is presented in table 3. Male sex and hypertension were more frequent in patients with non-lobar SICH, and diabetes mellitus, tobacco use, alcohol abuse and antithrombotic drug use were more frequent in patients with lobar SICH but none of these differences were statistically significant.

The prognosis of SICH by localisation is presented in table 4. No significant differences were found in 30-day case-fatality rates or the 6-month prognosis by localisation.

Table 1. Crude and age-adjusted incidence rates of first-ever lobar and non-lobar SICH by age groups and sex per 100,000 in Iquique, Chile, 2000–2002

	Person-years	Lobar		Non-lobar	
		n	rate	n	rate
Age groups					
0–34 years	245,516	1	0.4 (0–2.0)	1	0.4 (0–2.0)
34–44 years	62,300	2	3.2 (0.8–23.1)	3	4.8 (2.9–42.2)
45–54 years	43,174	1	2.3 (0.06–13)	13	30.1 (16–51.5)
55–64 years	23,682	7	29.6 (12–61)	11	46.5 (23.2–83)
65–74 years	13,838	3	21.7 (4.5–63)	4	29 (7.8–74)
75–84 years	6,366	1	15.7 (0.4–88)	9	141.4 (65–268)
≥85 years	1,836	0	0 (0–163)	2	109 (13–393.5)
Women	196,046	7	3.6 (1.4–7.3)	16	8.2 (4.7–13.2)
Men	200,466	8	6.0 (1.7–7.8)	27	13.5 (8.8–19.6)
All	396,712	15	3.8 (2.1–6.2)	43	10.8 (7.8–14.6)
Chile[1]			4.4 (3.3–5.5)		12.4 (10.5–14.3)
Europe[2]			6.2 (4.6–7.8)		17.6 (14.9–20.3)
USA[3]			5.7 (4.2–7.2)		17.2 (14.6–19.8)
World[4]			4.9 (3.6–6.2)		13.8 (11.7–15.9)
Women-adjusted[4]			3.9 (2.9–4.9)		10.0 (8.5–11.5)
Men-adjusted[4]			5.1 (3.8–6.4)		18.3 (15.5–21.1)

Values in parentheses denote 95% CI.
[1] Chile total population according to 2002 census. [2] Segi's European population. [3] USA 1990 population. [4] WHO world population.

Table 2. Incidence rates[1] of first-ever lobar and non-lobar SICH by age groups and sex per 100,000 in Iquique, Chile, 2000–2002

Age group years	Lobar (n = 15)		Non-lobar (n = 43)	
	men, rate	women, rate	men, rate	women, rate
<45	1.3 (0.1–4.6)	0.7 (0.01–4)	2.5 (0.7–6.5)	0 (0–2)
45–75	14.9 (5.5–32.5)	12.3 (4–28.8)	47.1 (28–73)	22.2 (10.2–42.2)
≥75	0 (0–100)	19.7 (0.5–113)	136.1 (37–349)	138.2 (56–285)

Values in parentheses denote 95% CI. [1] Person-years.

Discussion

In this Hispanic-Mestizo population, we found that the incidence of first-ever non-lobar SICH was almost three times that of lobar SICH. The age-adjusted incidence rates of non-lobar and lobar SICH were lower than those found in Hispanics in northern Manhattan by Sacco et al. [6]. In that study, the authors reported an incidence of 24.3 per 100,000 for non-lobar and 8.5 per 100,000 for lobar SICH in Caribbean Hispanics, higher than in whites (6.5 non-lobar and 6.0 lobar per 100,000), but lower than in blacks (31.2 non-lobar and 16.8 lobar per 100,000) [6]. Our findings are similar to those reported for whites in Greater Cincinnati (17.1 non-lobar and 9.4 lobar SICH per 100,000) and lower than those for blacks (33.2 non-lobar and 15.2 lobar per 100,000) [11]. The incidence of lobar SICH is also comparable to the 7 per 100,000 reported for Izumo in Japan, but that of non-lobar SICH is lower than the 23 per 100,000 reported there [25]. There are several possible reasons for lower incidence rates of both lobar and non-lobar

Table 3. Demographic, premorbid cardiovascular risk factors and antithrombotic medication by SICH localisation in Iquique, Chile

Variables	Lobar (n = 15)	Non-lobar (n = 43)	Risk ratio	95% CI	p
Mean age ± SD, years	57.4 ± 15	60.2 ± 14	–	–	0.51[1]
Male sex	8 (53.3; 26.6–78.7)	27 (62.8; 47.2–78.4)	0.8	0.5–1.4	0.55[2]
History of hypertension	7 (46.7; 21.3–73.4)	25 (58.1; 42.2–74.0)	0.8	0.4–1.4	0.55[2]
History of diabetes mellitus	4 (26.7; 7.7–55.1)	6 (14; 2.4–25.5)	1.9	0.6–5.8	0.42[2]
History of hypercholesterolaemia	3 (20; 4.3–48.1)	–	–	–	–
Any cardiopathy[3]	1 (6.7; 0.2–32.0)	2 (4.7; 0.6–15.8)	1.4	0.1–14	1.0[2]
Current smoker	4 (26.7; 7.8–55.1)	5 (11.6; 3.8–25.1)	2.2	0.7–7.4	0.2[2]
Heavy drinker	4 (26.7; 7.7–55.1)	6 (14; 2.4–25.5)	1.9	0.6–5.8	0.4[2]
Antiplatelets	3 (20; 4.3–48.1)	6 (14; 2.4–25.5)	1.4	0.4–5.0	0.6[2]
Oral anticoagulants	1 (6.7; 0.2–32.0)	2 (4.7; 0.6–15.8)	1.5	0.1–15	1.0[2]
Any antithrombotic drug use	4 (26.7; 7.7–55.1)	8 (20; 5.8–31.4)	1.4	0.5–4.0	0.7[2]

Numbers in parentheses are percentages and 95% CI.
[1] Unpaired t test. [2] Fisher's exact test. [3] Atrial fibrillation, coronary artery disease or congestive heart failure.

Table 4. Case-fatality rates at 30 days and outcome at 6 months by modified Rankin Scale of first-ever ICH by localisation in Iquique, Chile

	Prognosis							
	30 days		6 months					
	dead		independent[1]		dependent[2]		dead[3]	
	n	rate	n	rate	n	rate	n	rate
Lobar (n = 15)	6	40 (19–64)	4	26.6 (11–52.4)	5	33.3 (15.2–58.6)	6	40 (19–64)
Non-lobar (n = 42)[4]	12	28.6 (16.7–42.7)	16	37.2 (24.3–52.2)	12	27.9 (16.7–42.7)	14	32.5 (20.5–47.6)

Values in parentheses denote 95% CI.
[1] Modified Rankin score: 0–2. [2] Modified Rankin score: 3–5. [3] Modified Rankin score: 6. [4] One case with a non-lobar SICH localisation was lost to follow-up.

SICH in this population compared to Hispanics in the USA. It is possible the lower prevalence of risk factors associated with ICH plays an important role. The prevalence rates of hypertension and alcohol intake in this population were lower than those found in Hispanics in Manhattan where 76% had a history of hypertension and 22% of alcohol abuse [6]. They were also lower than in Hispanics with ICH in Nueces County, Texas, USA, where 75% were found to have a history of hypertension [10]. Our findings could truly reflect a lower population prevalence of hypertension in this region. In fact the national health survey performed in 2003 found that only 29.7% (95% CI: 19.7–39.7%) were hypertensive in the region where Iquique is located. It is also possible that there could be information and classification biases in the diagnosis of previous hypertension. Patients were considered hypertensive only if they had a history or were taking antihypertensive medication. It is possible that some hypertensive patients were misclassified as non-hypertensive if they or their relatives did not know their condition. In the national health survey in Chile only 60% of the hypertensive knew their condition, 33% were being treated and only 30% had normal values [26]. Alcohol intake was also lower in this population than in Hispanics in the USA. Risk factors for ICH associated with life style, such as high alcohol intake, have been found to be more prevalent in migrant compared to non-migrant populations [14]. Another possible explanation is that the city of Iquique is located in a relatively

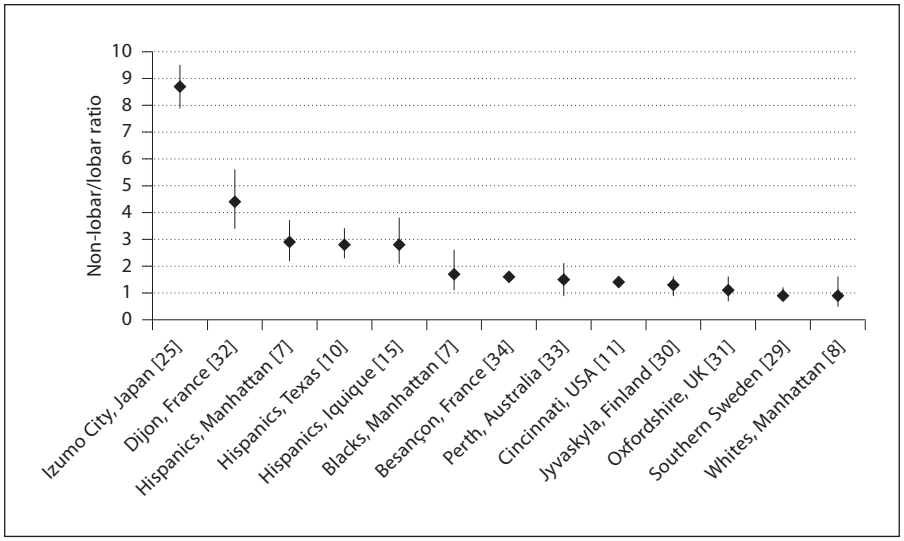

Fig. 2. Ratios of non-lobar to lobar ICH cases in different population-based studies.

wealthy region with a high socioeconomic status because of mining and fishing industries. At the time of this study it was the region of Chile with the third highest per capita income (USD 7,923), higher than the mean of the country (USD 6,680) in 2003. It has recently been reported that the gross national income per capita is independently associated with stroke burden and mortality [27], and that the socioeconomic level can explain up to a third of the differences in stroke prevalence in the USA [28]. It is also possible that our lower incidence is just pure chance because of the small sample size.

The ratio of non-lobar to lobar SICH in this population is similar to previous findings in Hispanic and black populations, lower than in Japanese and higher than in most white populations (fig. 2). Associations between ethnicity and SICH localisation have previously been reported [10, 35, 36]. Most of the differences could be related to the population prevalence of risk factors such as hypertension and alcohol abuse [37], and also to their treatment and control [9, 35, 38]. A higher risk of non-lobar SICH in Hispanics and blacks has also been attributed to a higher frequency of secondary causes of ICH such as AVM [39] or familial forms of cavernous angiomas [40]. Apolipoprotein polymorphisms of the E2 and E4 alleles have also been associated with SICH localisation, as well as untreated hypertension [41]. More recently, both E2 and E4 polymorphisms were associated with an increased risk of deep and cortical ICH, particularly in Asian patients [42].

In Iquique, the incidence of SICH increased with age, especially in non-lobar haemorrhages. A similar finding was reported for the Greater Cincinnati area [43]. In Sweden, lobar haematomas had a higher incidence than non-lobar ones at ages of ≥75 years [29]. In northern Manhattan and in Texas, Hispanics had an increased age-adjusted risk of non-lobar SICH compared to non-Hispanic whites [7, 10]. In this population, younger males had a higher incidence of non-lobar SICH between 45 and 75 years of age, and older women a higher risk of lobar SICH. This finding is similar to those reported by most population-based studies in white populations in northern Europe [29–31, 44], in Hispanics in the USA [7–10] and in black migrant populations in the UK [45].

We found no association between hypertension and SICH location, probably due to the small sample size. Many previous population-based studies have shown that hypertension is significantly and independently associated with non-lobar SICH [32, 46, 47]. A recent pooled analysis of population-based studies showed only a modestly significant association between hypertension and non-lobar ICH [48]. Diabetes was more frequent in lobar SICH in Iquique, but not significantly. Previous evidence has been conflicting. Diabetes was associated with non-lobar SICH in Malmö, Sweden [29]. In northern Manhattan, no association between SICH localisation and previous diabetes was found [7]. Similarly to other studies, heavy drinkers in Iquique had a non-significantly higher risk of lobar SICH [7]. We found a non-significant association between antithrombotic drug use and lobar SICH, as reported in other studies [31].

Overall, the prognosis of SICH by localisation was similar in this population. The same lack of an association with prognosis was observed in Manhattan [7], Tex-

as [10] and Perth, Australia [33], while a better outcome was reported in lobar SICH in Besançon, France [34].

Our study has several strengths. It was population based, including hospitalised and non-hospitalised patients. It had a high rate of early CT scans, the allocation according to localisation was blinded to the history of hypertension, and it included all age groups.

It also has limitations. The most important is the small sample size, and thus the wide CI around the point estimates of incidence in the subgroups and the probability of missing significant associations. Furthermore, a classification bias could have been introduced as we were not able to allocate 6 ICH cases to a specific localisation. We excluded secondary ICH cases from the analyses, which limits their comparability to a few studies.

Conclusion

The incidence of non-lobar SICH was high, but not as high as that in Hispanics in northern Manhattan, blacks in Cincinnati and Japanese in Izumo. Young males had higher incidences of non-lobar SICH compared to women. The non-lobar-to-lobar ratio was similar to previous findings in Hispanic populations. No risk factor was associated with a particular localisation although hypertension was more frequent in non-lobar SICH, whereas diabetes, heavy drinking and antithrombotic drug use was more frequent in lobar SICH. The prognosis was similar for both localisations.

Acknowledgements

P.M.L. has received research grants, research support and travel grants by Sanofi-Synthelabo Chile, Boehringer Ingelheim and Glaxo Smith Kline. C.S. has received research support and travel grants by Sanofi-Synthelabo Chile, Boehringer Ingelheim and Glaxo Smith Kline.

This investigation was possible thanks to the unconditional support of Sanofi-Aventis Chile, Glaxo Smith Kline and Boehringer Ingelheim.

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