Incidence and MRI patterns of acute ischemic stroke at a quaternary care hospital in Mexico City

Mariana López-Mejía,* Pedro Yeverino-Suárez, Ernesto Roldán-Valadez***

RESUMEN

Introducción. El accidente cerebrovascular es un déficit neurológico que se desarrolla rápidamente, presenta una alta tasa de mortalidad y puede inducir discapacidad a largo plazo. La resonancia magnética es una herramienta fundamental para el diagnóstico del ataque cerebral. Existe poca información acerca de la incidencia de accidente cerebrovascular y sus patrones de resonancia magnética en centros especializados en América Latina. **Material y métodos.** Se realizó un estudio retrospectivo, incluyendo pacientes con diagnóstico clínico de accidente cerebrovascular a su admisión en la Sala de Urgencias y con confirmación del diagnóstico por resonancia magnética. Los pacientes fueron reclutados de enero 2011 a diciembre 2012. **Resultados.** 238 pacientes fueron ingresados con síntomas de accidente cerebrovascular, 124 se sometieron a resonancia magnética con 76 confirmaciones. La distribución por edad y género fue de 42 hombres (65.38 ± 15.85 años, rango 33-91 años) y 34 mujeres (69.47 ± 12.08 años, rango 31-89 años). Se encontró una incidencia anual neta de 119.84 por cada 100,000 casos de accidente cerebrovascular agudo con una razón hombre:mujer de 1.2:1, con 64% de los pacientes incluidos entre los 65-74 y 75-84 grupos de edad. Se confirmaron los patrones de resonancia magnética de reportes anteriores: la arteria cerebral media fue la más afectada con 69.74% (χ^2 = 104,216, p < 0,001); donde la disminución del flujo era más común que la oclusión de los vasos (47.37% *vs.* 30.26%); 71.62% de los casos tenían < 1/3 de la participación de la red arterial (χ^2 = 73,324, p < 0,001). Los infartos pequeños (< 70 cm^3) representaron 71.23% de los casos (χ^2 = 13,164, p < 0.001). **Conclusión.** La tasa de incidencia de los accidentes cerebrovasculares en nuestro centro es más bajo que en algunos países desarrollados. Las tasas más altas pueden reflejar un mejor diagnóstico y mayor conocimiento de la gente acerca de accidente cerebrovascular. La resonancia magnética en instalaciones especializadas puede ayudar a enfocar las estrategias trombolíticas en pacientes seleccionados.

Palabras clave. Accidente cerebrovascular. Incidencia. Resonancia magnética. Perfusión. Difusión.

ABSTRACT

Introduction. Stroke is a rapidly neurological deficit with a high mortality rate and can induce long-term disability. MRI is a fundamental image tool for ischemic stroke diagnosis. There is still scarce information about the stroke incidence and its MRI patterns in specialized centers in Latin America. **Material and methods.** Retrospective study of patients with clinical diagnosis of stroke on admission at the Emergency Room with brain MRI confirmation. Patients were recruited from January 2011 to December 2012. **Results.** 238 patients were admitted with symptoms of stroke, 124 underwent brain MRI with 76 confirmations. The age distribution was 42 men (65.38 ± 15.85 years; range 33-91 years) and 34 women (69.47 ± 12.08 years, range 31-89 years). We found a crude annual incidence rate of 119.84 per 100,000 cases of acute ischemic stroke with a male to female ratio of 1.2:1, with 64% of patients included in the 65-74 and 75-84 age groups. We confirmed previously reported MRI patterns: middle cerebral artery was the most commonly affected one with 69.74% (χ^2 = 104.216, p < 0.001); decreased flow was more common than vessel occlusion (47.37 *vs.* 30.26%); 71.62% of cases had < 1/3 involvement of arterial territory (χ^2 = 73.324, p< 0.001). Small infarcts (< 70 cm^3) accounted for 71.23% of cases (χ^2 = 13.164, p < 0.001). **Conclusion.** The incidence rate in our center is lower than some developed countries, higher rates can reflect an improvement in awareness of people about stroke; information about MRI patterns in specialized facilities could help in tailoring thrombolytic strategies for selected patients.

Key words. Ischemic stroke. Incidence. MRI. Perfusion. Diffusion.

*Magnetic Resonance Unit, **Emergency Department. Medica Sur Clinic & Foundation. Mexico City. Mexico.

Correspondence:
Ernesto Roldán-Valadez, M.D., M.Sc.
Magnetic Resonance Unit, Medica Sur Clinic & Foundation
Puente de Piedra, No. 150. Col. Toriello Guerra. Deleg. Tlalpan. C.P. 14050. México, D.F.
Tel.: (52-55) 5666-1765. Fax: (52-55) 5424-4429
E-mail: ernest.roldan@usa.net

INTRODUCTION

Comparing stroke rates and patterns in different parts of the world and at different points in time may increase our understanding of this disease. Stroke is defined as a rapidly developed global or focal neurological deficit lasting more than 24 h or leading to death with no apparent cause other than vascular origin.[1] Stroke will be a public health problem in Latin America during the next decades because of an increase in life expectancy, changes in the lifestyle of the population and the increase in incidence of diseases such as metabolic syndrome, diabetes and hypertension in most of the countries in this geographical area. Because epidemiological and clinical characteristics of stroke vary according to environmental, racial, and sociocultural factors, we need to be aware of the peculiarities of stroke on this continent to reduce the impact burden of this epidemic.[2]

For health policy planning, it is imperative to understand projected future prevalence and cost of stroke in each country and to identify potential actions that might reduce this burden. Currently, stroke is the fourth leading cause of death in the United States and a leading cause of disability.[3] The cost of treating stroke victims is expected to soar in the next two decades, according to a study by the American Heart Association and the American Stroke Association with real total direct annual stroke-related medical costs expected to increase from $72 billion to $183 billion (2010 dollars) between 2012 and 2030.[3]

The burden of prolonged hospitalization on the family of stroke patients, the aftermath of disability from the disease, and the economic implication on survival of stroke patients, as well as the overstretching of health facilities have been previously explored.[4] However, some basic demographics features and magnetic resonance imaging (MRI) patterns in patients undergoing acute ischemic stroke (AIS) are missing in the current literature, specifically data from facilities considered to be quaternary care hospitals. This concept refers to hospitals with advanced levels of medicine, which are highly specialized and not widely accessed. Experimental medicine and some types of uncommon diagnostic (diffusion-perfusion analysis of MRI images for our study) or surgical procedures are considered quaternary care; a quaternary care hospital may have virtually any procedure available, whereas a tertiary care facility may not offer a sub-specialist with that training. These services are usually only offered in a limited number of regional or national health care centers.[5]

Although stroke affects both gender and is increasingly common from the sixth decade, with young patients not being exempted;[6] we have noticed that most centers cover only a limited age range, monitoring stroke up to age 65 years and none routinely collecting data on those older than 75 years, in whom the incidence of stroke might be highest.[7] The areas of the world covered by these studies are still very limited, and reliable information remains sparse for nonwhite populations.

Recent studies comparing the age-adjusted incidence between Hispanic- and white-populations showed significant differences in first ischemic stroke as 140 to 168 per 100,000 *vs.* 88 to 136 per 100,000.[6,8-10] It is accepted than an "ideal" stroke incidence study does not exist, but studies closely approaching it will reveal the most reliable and comparable results. There is a need for further studies to fill the gaps of the worldwide incidence of stroke, particularly for developing countries.[7] For example, information about the incidence rates of AIS in young and older Mexican patients from tertiary or quaternary care hospitals is missing in the medical literature to the best of our knowledge.

The aims of this study were focused in review the incidence rates and MRI patterns of AIS in a quaternary-care hospital in Mexico City and make comparisons with what has been documented on the disease in urban settings from other countries.

MATERIAL AND METHODS

Study design

This was a retrospective study carried out at Medica Sur Clinic & Foundation, in Mexico City. This study belongs to a research line trying to identify MRI predictive biomarkers in the evaluation of AIS, the main protocol for this research received previous approval by the Institutional Review Board (2010-EXT-05). The facility fulfills the requisites to be considered a quaternary-care private hospital in the south of Mexico City. The hospital runs several postgraduate training programs such as internal medicine and a fellowship in whole-body MRI. There are consultant neurologists available at any time, and the hospital has the possibility to perform advance magnetic resonance imaging analyses such as diffusion and perfusion.

Clinical and imaging definitions of stroke

We use the World Health Organization (WHO) definition of stroke, "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than

24 h or leading to death with no apparent cause other than that of vascular origin" as it is and accepted standard.[7]

In the last decade, an advanced MRI technique known as diffusion-weighted imaging (DWI) added another dimension to diagnostic imaging improving the diagnostic yield while being practical and feasible.[11] DWI measures the net movement of water in tissue due to random (Brownian) molecular motion of water and shows hyperintense ischemic tissue changes within minutes to a few hours after arterial occlusion due to a reduction of the apparent diffusion coefficient (ADC).[12] The ADC reduction occurs primarily in the intracellular space associated with disruption in membrane ionic homeostasis and cytotoxic edema. A decreased ADC and increased signal on DWI (described in MRI reports as hyperintense focal region) represent irreversible ischemia; the combination of DWI, ADC maps and T2-weighted images allows differentiating acute from subacute or older AIS lesions.[13]

DWI has emerged as the most sensitive and specific imaging technique for acute infarct, far better than non-enhanced computed tomography or any other MRI sequence (Figure 1A). It has a high sensitivity (88 to 100%) and specificity (95 to 100%) for detecting infarcted regions, even at very early time points,[14,15] within minutes of symptoms onset.[14,16] Thus, early after ischemia onset, the visible diffusion lesion will include both regions of irreversible infarction with more severe ADC changes and regions of salvageable penumbra with less severe ADC changes (Figure 1B).

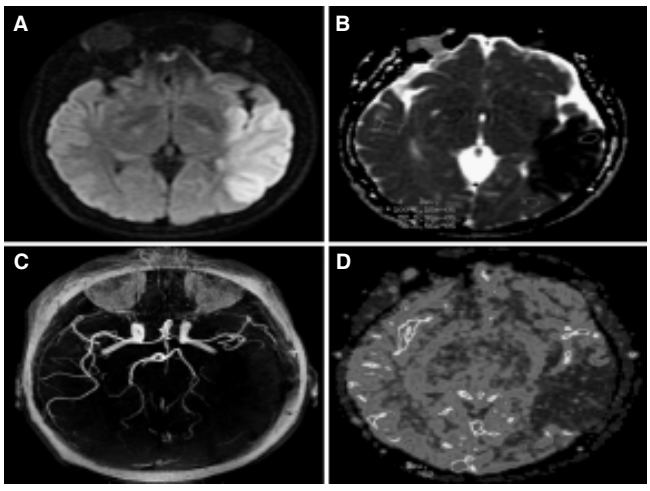

Figure 1. A-D. MRI sequences in the assessment of acute ischemic stroke. **A.** Axial plane showing infarcted brain tissue in a diffusion-weighted image. **B.** Apparent diffusion coefficient map showing a restricted diffusion. **C.** 3D time-of-flight MR angiography shows the occlusion of M2 left segment of the middle cerebral artery. **D.** Cerebral blood flow (CBF) map depicts a decreased perfusion in the infarcted tissue.

Patients, inclusion and exclusion criteria

We retrieved and reviewed the medical case records of all patients who had a clinical diagnosis of stroke (or similar diagnosis as: probable stroke, ischemic stroke, lacunar stroke, hemorrhagic stroke, basilar stroke) whom arrived to the ER from January 2011 to December 2012. The inclusion criterion was *First-Ever-in-a-Lifetime* stroke, because it most closely reflects important determinants of disease etiology. Patients with TIA (i.e. a neurological deficit lasting < 24 h with no stroke found on brain imaging) or prior stroke were excluded.[17]

Only those cases that had complete information, met the WHO clinical criteria for diagnosis and had an MRI study for confirmation of diagnosis were considered. The digital MRI records of patients with inclusion criteria were reviewed to acquire necessary data for the image pattern analysis.

Standard data presentation and risk measures

We collected data over complete years to avoid confounding from the possible effect of seasonal variations in incidence, which was documented in several community-based studies.[9,18] Considering previous stroke epidemiologic studies used mid-decade 10-year age bands we retain this convention in our study.[7]

Dividing the number of cases of first-ever stroke by the number of screened individuals older than 18 years during the observed time period, allowed us to calculate the crude stroke annual incidence rate per 100,000 population, this measure of risk has been previously reported.[2]

We additionally calculated an age-adjusted incidence rate using mid-decade 10-year age bands (25 to 34, 35 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84 and 85 to 94 years).[19]

Statistical analysis

Descriptive and frequency statistics were obtained for the variables of interest. Chi square was used to test for statistical significance between categorical variables, t-test was used in continuous variables. A P value < 0.05 was considered statistically significant. All analyses were carried out using the IBM® SPSS® Statistics software (version 22.0.0.0 IBM Corporation; Armonk, New York, USA). General presentation of the manuscript followed the guidelines set by the International Committee of Medical Journal Editors.[20]

Table 1. Crude annual incidence rate of acute ischemic stroke grouped by age.

Data collection year	Age-group	Population, n (%)	Age-adjusted incidence by age-group (cases per 100,000)
2011-2012	25-34	3 (4)	4.73
	35-44	5 (7)	7.88
	45-54	9 (12)	14.19
	55-64	8 (11)	12.62
	65-74	24 (32)	37.85
	75-84	24 (32)	37.85
	85-94	3 (4)	4.73
	Total	76 (100)	119.84

Table 2. Annual incidence rate of acute ischemic stroke grouped by age and gender with 95% CI.

	Males			Females		
	Incidence	95% CI		Incidence	95% CI	
Age-group	rate	Lower bound	Upper bound	rate	Lower bound	Upper bound
25-34	4.8	4.308	5.291	1	0.508	1.4916
35-44	11.9	11.408	12.391	-	-	-
45-54	11.9	11.408	12.391	4	3.508	4.491
55-64	14.3	13.808	14.791	2	1.508	2.491
65-74	21.4	20.908	21.891	15	14.508	15.491
75-84	33.3	32.808	33.791	10	9.508	10.491
85-94	2.4	1.908	2.891	2	1.508	2.491

RESULTS

Demographic data

During a two-years period (2011-2012), 31,708 individuals underwent admission in the ER, 238 subjects were clinically diagnosed to have stroke, 124 patients undergone brain MRI with 76 MRI diagnoses of AIS. This number accounted for 0.75% of total medical admissions to the ER over the same period. This gave a crude annual incidence rate of 119.84 cases of AIS per 100,000.

We found a gender and age distribution of 42 men (65.38 ± 15.85 M, SD; range 33-91 years) and 34 women (69.47 ± 12.08 years, range 31-89), giving a ratio of male to female 1.2:1; that is, we observed a strong preponderance of male stroke patients which was not statistically significant $\chi^2 = 0.842$, $p = 0.359$. The age distribution spread over a 7 mid-decades, with 64% of patients in the 65-74 and 75-84 age groups, this represent a significant difference $\chi^2 = 70.145$, $p = < 0.001$. Table 1 depicts the incidence rate by age groups and figure 2 shows the age distribution using mid-decade 10 year-age bands. Table 2 shows the annual incidence rate grouped by age group and gender with 95% CI.

MRI patterns in AIS

We found a non-significant trend regarding the affected side of cerebral hemispheres in both genders with the left hemisphere being more frequently affected then the right one $\chi^2 = 0.111$, $p = 0.139$, for males; and $\chi^2 = 0.947$, $p = 0.330$ for females; figure 3 shows the hemisphere distribution for each gender.

The more frequently affected artery was the middle cerebral artery (MCA) 69.74%, followed by the posterior cerebral artery (PCA) 11.84%, and the basilar artery 10.53%. Less than 8% of cases were distributed among the rest of arteries of the Willis polygon. These differences were significant $\chi^2 = 104.216$, $p \leq 0.001$; figure 4A presents the affected arteries.

There was an unequal distribution in the decrement of arterial blood flow observed for all patients, 35 (47.37%) had decreased flow, 26 (30.26%) occluded and 13 (22.37%) had normal arterial flow evaluated in the 3D time-of-flight MR angiography; this findings had statistical significance, $\chi^2 = 9.919$, $p = 0.007$. Figure 4B shows the decrement in arterial blood flow.

Considering the infarct extension, 71.62% of patients showed less than 1/3 involvement of affected territory; 24.32% showed 2/3 of the arterial affected territory, and only 4% presented a full affection of the arterial territory

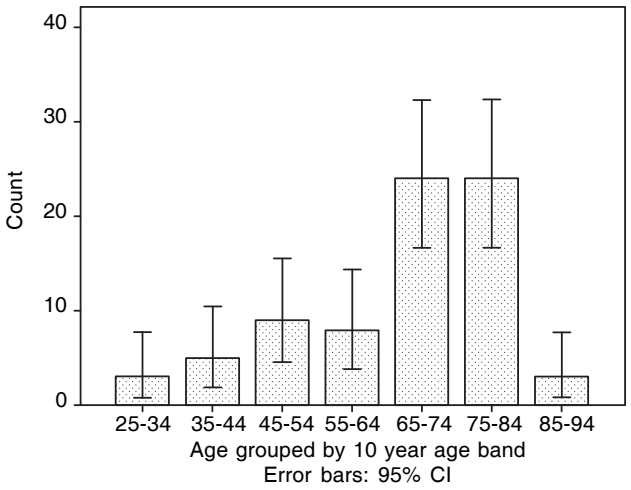

Figure 2. Age distribution in acute ischemic stroke using mid-decade 10 year-age bands.

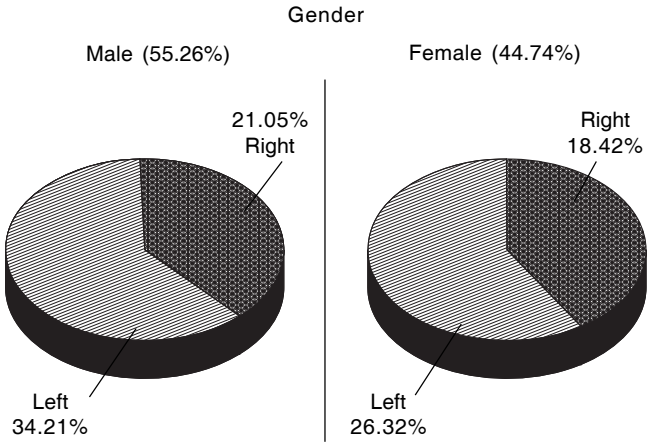

Figure 3. Percentage of cerebral hemisphere affection in each gender in acute ischemic stroke. Affected hemisphere.

involved. This finding had a significant difference $\chi^2 = 73.324$, $p \leq 0.001$; figure 4C depicts the percentages of infarct extension.

Our last variable in the MRI pattern analysis involved the calculation of the infarct size by measuring the cm^3 of each infarct in the DWI sequence. We found 71.23% of cases corresponding to infarcts with small volume (< 70 cm^3) and 28.77% of infarct with a large volume (< 70 cm^3). These values represent a significant difference, $\chi^2 = 13.164$, $p \leq 0.001$; figure 4D shows the percentages of volume distribution.

DISCUSSION

The incidence and imaging patterns of AIS in Mexico have not been widely studied to the best of our knowledge, the reports about the incidence of AIS for Hispanics is limited as well, this scarce evidence compelled us to report the findings from a quaternary care hospital focusing only on the AIS incidence of patients that arrived to the ER.

The annual crude incidence we found, 119 per 100,000, can be considered an intermediate value between those reported by some Latin-American countries: one of the first studies designed to assess stroke epidemiology was performed in Cuzco, Peru; it reported a crude annual incidence rate (first-ever stroke) of 183 per 100,000 (1995);[21] another study reported in the city of Sabaneta, Colombia; found and annual incidence rate of stroke of 89 per 100,000 (1993).[22]

In European countries, the stroke incidence has reported higher rates, with significant differences between gender, among men of all ages stroke ranged from 124 per 100,000 in South London (2003) to 185 per 100,000 in the Scottish Borders region (1998); and among women, incidence ranged from 88 to 146 per 100,000 in the same respective studies. Incidence in studies set in Oxfordshire and East Lancashire were similar, ranging from 135 to 152 per 100,000 among males.[19]

A lower stroke prevalence in Latin-American countries compared than that from developed countries have previously been reported probably because of some unknown protective ethnic factors or differences in dietary habits or lifestyles.[21,22] This hypothesis is supported by the finding that stroke prevalence is even lower in rural than in urban areas. The low incidence rate has also been related to the implementation of campaigns directed at teaching the community about the hazards of stroke risk factors.[2]

Our finding of a strong preponderance of male stroke patients have been recently reported in German, China and Indian datasets.[23] It is both of clinical and sociocultural importance to investigate the causes for gender gap in stroke patients- to guarantee that both female and male patients have equal access to in-hospital medical care and to further enlighten gender-specific differences in stroke. So far, the gender ratio of the general population and gender-specific stroke incidence rates are likely to be the major determinants, but sociocultural peculiarities may also play a crucial role.[23]

Compared with Asia, our incidence rate was very similar to that one reported in the city of Birjand, Iran of 103.4 cases per 100,000 (2008) this study was performed in a tertiary care hospital.[24] We believe that a higher incidence rate can reflect an improvement in awareness of people

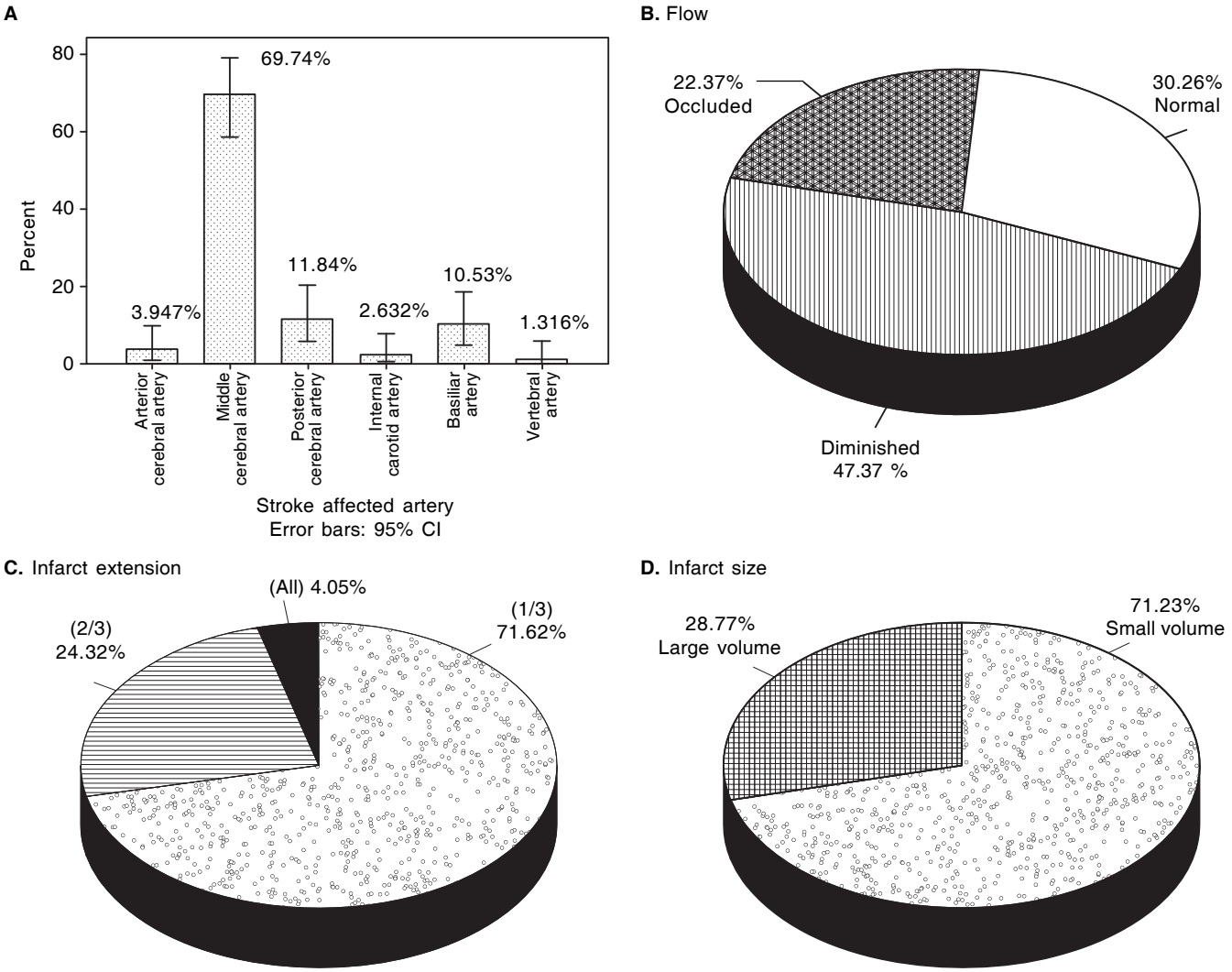

Figure 4. MRI patterns in acute ischemic stroke (AIS). **A.** Percentage of affection in the Willis polygon. **B.** Degree of blood flow.

about stroke and its signs or symptoms as well as more feasible and facile accessibility to health care centers, which both can raise the number of referred patients to tertiary care hospitals.

Some limitations in this study need to be addressed: this was an observational study, which limited the inferences that can be made about etiological relationships. Also, poor or incomplete medical record keeping, missing data and lack of essential, specific imaging diagnostic studies were present. Despite these limitations, we have been able to review the incidence and imaging pattern of stroke in selected patients. In addition, although great measures were taken to include all incident stroke cases, in any incidence study, complete capture of all cases cannot be substantiated. The fact that not all subjects underwent a systematic investigation could be a source of information bias. However, our study provides important data for specialized stroke centers.

In conclusion, our findings of incidence and imaging patterns lead us to consider the fact that the knowledge and perception of stroke risk factors and its warning sign can be increased in the hospital patients and health workers, as it has been observed in other centers.[25] Further studies about imaging patterns are necessary in order to correlate these findings in the context of knowledge of race and sex differences in disease biology; these will help

to assess the importance of other putative explanations for race and sex disparity, such as exclusion from care on "socioeconomic rather than clinical grounds". Also, regional reports of subtype-specific age- and sex-adjusted incidence rates for AIS would permit the development of community-friendly intervention programs aimed at preventing and modifying the risk factors in persons prone to diseases in tertiary and quaternary care hospital. These programs might eventually be incorporated into healthcare system, so that they are recognized early and effectively managed. Lastly, it's also important to emphasize the need of implementation of the Stroke Guidelines recommended by the American Heart Association/American Stroke Association (AHA/ASA), so that, in the absence of enough formal Stroke Units in Latin America, the ER in as many as possible hospitals would be able to attend patients with AIS or TIA according to international standards.

ABBREVIATIONS

- **ADC:** apparent diffusion coefficient.
- **AHA/ASA:** American Heart Association/American Stroke Association.
- **AIS:** acute ischemic stroke.
- **DWI:** diffusion-weighted imaging.
- **ER:** emergency room.
- **MCA:** middle cerebral artery.
- **MRI:** magnetic resonance imaging.
- **PCA:** posterior cerebral artery.
- **WHO:** World Health Organization.

REFERENCES

1. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ* 1980; 58(1): 113-30. PubMed PMID: 6966542. Pubmed Central PMCID: 2395897. Epub 1980/01/01. eng.
2. Saposnik G, Del Brutto OH, Iberoamerican Society of Cerebrovascular D. Stroke in South America: a systematic review of incidence, prevalence, and stroke subtypes. *Stroke; a journal of cerebral circulation* 2003; 34(9): 2103-7. PubMed PMID: 12907823.
3. Ovbiagele B, Goldstein LB, Higashida RT, Howard VJ, Johnston SC, Khavjou OA, et al. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. *Stroke; a journal of cerebral circulation* 2013; 44(8): 2361-75. PubMed PMID: 23697546.
4. Ogun SA, Ojini FI, Ogungbo B, Kolapo KO, Danesi MA. Stroke in south west Nigeria: a 10-year review. *Stroke; a journal of cerebral circulation* 2005; 36(6): 1120-2. PubMed PMID: 15879325. Epub 2005/05/10. eng.
5. Lai JC, Montero A, Lebwohl B, Brown RS, Jr. A novel housestaff educational model for quaternary-care patients at an academic health center. *Academic medicine: journal of the Association of American Medical Colleges* 2009; 84(2): 206-11. PubMed PMID: 19174667.
6. Desalu OO, Wahab KW, Fawale B, Olarenwaju TO, Busari OA, Adekoya AO, et al. A review of stroke admissions at a tertiary hospital in rural Southwestern Nigeria. *Annals of African Medicine* 2011; 10(2): 80-5. PubMed PMID: 21691011.
7. Sudlow CL, Warlow CP. Comparing stroke incidence worldwide: what makes studies comparable? *Stroke; a journal of cerebral circulation* 1996; 27(3): 550-8. PubMed PMID: 8610328.
8. Morgenstern LB, Smith MA, Lisabeth LD, Risser JM, Uchino K, Garcia N, et al. Excess stroke in Mexican Americans compared with non-Hispanic Whites: the Brain Attack Surveillance in Corpus Christi Project. *Am J Epidemiol* 2004; 160(4): 376-83. PubMed PMID: 15286023. Pubmed Central PMCID: 1524675. Epub 2004/08/03. eng.
9. Ricci S, Celani MG, Vitali R, La Rosa F, Righetti E, Duca E. Diurnal and seasonal variations in the occurrence of stroke: a community-based study. *Neuroepidemiology* 1992; 11(2): 59-64. PubMed PMID: 1495575.
10. Gillum RF. Epidemiology of stroke in Hispanic Americans. *Stroke; a journal of cerebral circulation* 1995; 26(9): 1707-12. PubMed PMID: 7660419. Epub 1995/09/01. eng.
11. Warach S. Stroke neuroimaging. *Stroke; a journal of cerebral circulation* 2003; 34(2): 345-7. PubMed PMID: 12574531.
12. Liu Y, Laakso MP, Karonen JO, Vanninen RL, Nuutinen J, Soimakallio S, et al. Apolipoprotein E polymorphism and acute ischemic stroke: a diffusion- and perfusion-weighted magnetic resonance imaging study. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 2002; 22(11): 1336-42. PubMed PMID: 12439291.
13. Schellinger PD, Bryan RN, Caplan LR, Detre JA, Edelman RR, Jaigobin C, et al. Evidence-based guideline: The role of diffusion and perfusion MRI for the diagnosis of acute ischemic stroke: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2010; 75(2): 177-85. PubMed PMID: 20625171. Pubmed Central PMCID: 2905927.
14. Barber PA, Darby DG, Desmond PM, Gerraty RP, Yang Q, Li T, et al. Identification of major ischemic change. Diffusion-weighted imaging versus computed tomography. *Stroke; a journal of cerebral circulation* 1999; 30(10): 2059-65. PubMed PMID: 10512907.
15. Gonzalez RG, Schaefer PW, Buonanno FS, Schwamm LH, Budzik RF, Rordorf G, et al. Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. *Radiology* 1999; 210(1): 155-62. PubMed PMID: 9885601.
16. Ay H, Buonanno FS, Rordorf G, Schaefer PW, Schwamm LH, Wu O, et al. Normal diffusion-weighted MRI during stroke-like deficits. *Neurology* 1999; 52(9): 1784-92. PubMed PMID: 10371524.
17. White H, Boden-Albala B, Wang C, Elkind MS, Rundek T, Wright CB, et al. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation* 2005; 111(10): 1327-31. PubMed PMID: 15769776. Epub 2005/03/17. eng.
18. Shinkawa A, Ueda K, Hasuo Y, Kiyohara Y, Fujishima M. Seasonal variation in stroke incidence in Hisayama, Japan. *Stroke; a journal of cerebral circulation* 1990; 21(9): 1262-7. PubMed PMID: 2396260.

19. Bhatnagar P, Scarborough P, Smeeton NC, Allender S. The incidence of all stroke and stroke subtype in the United Kingdom, 1985 to 2008: a systematic review. BMC public health. 2010;10:539. PubMed PMID: 20825664. *Pubmed Central PMCID*: 2944372.
20. Uniform requirements for manuscripts submitted to biomedical journals: Writing and editing for biomedical publication. *Journal of pharmacology & pharmacotherapeutics* 2010; 1(1): 42-58. PubMed PMID: 21808590. Pubmed Central PMCID: 3142758.
21. Jaillard AS, Hommel M, Mazetti P. Prevalence of stroke at high altitude (3380 m) in Cuzco, a town of Peru. A population-based study. *Stroke; a journal of cerebral circulation* 1995; 26(4): 562-8. PubMed PMID: 7709397.
22. Uribe CS, Jimenez I, Mora MO, Arana A, Sanchez JL, Zuluaga L, et al. Epidemiology of cerebrovascular diseases in Sabaneta, Colombia (1992-1993). *Revista de Neurología* 1997; 25(143): 1008-12. PubMed PMID: 9280623. Epidemiologia de las enfermedades cerebrovasculares en Sabaneta, Colombia (1992-1993).
23. Foerch C, Ghandehari K, Xu G, Kaul S. Exploring gender distribution in patients with acute stroke: A multi-national approach. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences* 2013; 18(1): 10-6. PubMed PMID: 23901335. Pubmed Central PMCID: 3719219.
24. Dehghani Firoozabadi M, Kazemi T, Sharifzadeh G, Dadbeh S, Dehghan P. Stroke in Birjand, Iran: a hospital-based study of acute stroke. *Iranian Red Crescent medical journal* 2013; 15(3): 264-8. PubMed PMID: 23984011. Pubmed Central PMCID: 3745760.
25. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. *Stroke; a journal of cerebral circulation* 2009; 40(4): 1032-7. PubMed PMID: 19211484. Pubmed Central PMCID: 2676725. Epub 2009/02/13. eng.