



ORIGINAL ARTICLE

Etiology and risk factors for a first episode of cerebral ischemia in young adults

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KEYWORDS

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Abstract

Introduction: To determinate the etiology and risk factors for a first episode of cerebral ischemia in young adults at three hospitals of Lima and Callao-Peru.

Methods: Multicentric study carried out at three national hospitals in Lima. The sample included 30 patients with a first episode of stroke and 60 controls matched by age and sex 2:1 with the patients. Serum biochemistry studies, EKGs and echocardiograms were done. Etiologies were classified based on the classification of Baltimore-Washington Cooperative Young Stroke Study.

Results: The most frequent etiologies were cardiac embolism and atherosclerotic valvular heart disease, which were 30% of the cases (9 patients) each one. Hypertriglyceridemia ($p=0.014$), valvular heart disease ($p=0.001$) and hormonal contraception/replacement therapy ($p=0.002$) were independent risk factors for a first episode of cerebral ischemia in peruvian young adults. Motor deficiency was the most frequent presentation (50.0%). Intracranial hypertension and urinary tract infection were the most frequent complications during acute ischemia and mortality was raised up to 10%.

Conclusions: The hypertriglyceridemia, valvular heart disease and the use of oral contraceptives are independent risk factors for a first episode of ischemia in young adults from three hospitals of Lima and Callao. The most frequent etiologies were cardiac embolism and atherosclerotic valvular heart disease.

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PALABRAS CLAVE

Isquemia cerebral;
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Factores de riesgo;
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Etiología y factores de riesgo para un primer episodio de isquemia cerebral en adultos jóvenes**Resumen**

Introducción: Determinar la etiología y factores de riesgo para un primer episodio de isquemia cerebral en adultos jóvenes de tres hospitales de Lima y Callao-Perú.

Métodos: Estudio de casos y controles, multicéntrico realizado en el Hospital Nacional Dos de Mayo, Hospital Nacional Daniel Alcides Carrión y Hospital EsSalud Alberto Sabogal Sologuren. La muestra estuvo constituida por 30 pacientes con un primer episodio de enfermedad cerebrovascular y 60 controles pareados por edad y sexo 2:1 con los pacientes. A todos se les realizó estudios de bioquímica sérica y evaluación cardiovascular (electrocardiograma y ecocardiografía). Las etiologías fueron clasificadas de acuerdo a la clasificación de *Baltimore-Washington Cooperative Young Stroke Study*.

Resultados: Las etiologías más frecuentes fueron el cardioembolismo y la vasculopatía aterosclerótica con un 30% de casos (9 pacientes) cada uno. Los factores de riesgo independientes para un primer episodio de isquemia cerebral fueron la hipertrigliceridemia ($p = 0,014$), la enfermedad valvular cardíaca ($p = 0,001$) y la anticoncepción/ reemplazo hormonal ($p = 0,002$). El déficit motor fue la forma de presentación más frecuente (50,0%); la hipertensión endocraneana y la infección del tracto urinario fueron las principales complicaciones durante el episodio agudo y la mortalidad fue del 10%.

Conclusiones: La hipertrigliceridemia, enfermedad valvular cardíaca y el uso de anticonceptivos/ reemplazo hormonal constituyen factores de riesgo independientes para un primer episodio de isquemia en adultos jóvenes de tres hospitales de Lima y Callao, siendo las etiologías más frecuentes el cardioembolismo y la vasculopatía aterosclerótica.

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Introduction

Cerebrovascular disease (CVD) is defined as the presence of clinical signs of brain function alteration that develop quickly, last longer than 24 hours, or lead to death without any other evident causes than vascular origin.¹ In recent years, it has become one of the major causes of morbidity and mortality in developed and developing countries.¹⁻³ It is considered to affect mostly people over the age of 75.² However, 5%-15% of patients are under 50,^{1,3-6} with ischemic cerebrovascular disease being predominant in this age group.^{1,7-9}

Cerebral ischemia in young adults can reduce life expectancy and quality, causing disability in a great portion of patients who survive, as well as social, economic and emotional repercussions in the victims, their families and the community.^{2,5} Studies have shown a range of aetiologies⁹ with great variations among countries, mostly in relation to the population studied.^{1,4,7,10-14} Furthermore, diverse criteria are used for its classification, with the most important ones being *Trial of ORG 10172 in Acute Stroke Treatment* (TOAST) and the *Baltimore Washington Cooperative Young Stroke Study*.^{11,15-17}

Risk factors for CVD are dyslipidemia, obesity, hypertension, diabetes mellitus, cardiovascular disease, migraine, hormonal contraception, drug addiction, alcoholism, acute alcohol intake, smoking and illicit drug use (cocaine and marijuana), with ample variations according to the geographic location and the diagnostic criteria used.^{1,18-25}

In Peru and in all of South America, there are few investigations published about CVD in young adults. That is why the objective of this study was to determine the

aetiology and risk factors for first episodes of cerebral ischemia in young adults in 3 hospitals in Lima and Callao (Peru).

Materials and method**Design, population and sample**

The study of cases and controls was carried out between July 2004 and December 2005. The sample consisted of 30 patients diagnosed with a first episode of ischemic CVD (group of cases), all taken from the Hospital Nacional Dos de Mayo (Lima, Peru), Hospital Nacional Daniel Alcides Carrión (Callao, Peru) and Hospital EsSalud Alberto Sabogal Sologuren (Callao, Peru); at the same time, we recruited 60 healthy subjects (control group) paired according to age and gender (2 controls for every patient) with the group of cases. The selection criteria were the following:

Case group

Inclusion criteria:

1. Patients between the ages of 18 and 50, of any gender.
2. A case of first episode of cerebral ischemia.

The exclusion criteria were: 1) haemorrhagic CVD; 2) transient cerebral ischemia; and 3) not agreeing to participate in the study voluntarily.

Control group

Inclusion criteria:

1. Clinically healthy individuals, picked from the community, between the ages of 18 and 50, paired according to age and gender with the group of cases.

Exclusion criteria were: 1) individuals who did not voluntarily agree to be part of the study; and 2) individuals with a family or personal history of CVD.

Technique and method

Patients with a first episode of cerebral ischemia were examined by a neurologist and a resident physician who assessed the possible risk factors such as LDL dyslipidemia, HDL dyslipidemia, hypertriglyceridaemia, diabetes mellitus, arterial hypertension, cardiovascular disease, smoking, alcoholism, consumption of illicit drugs (cocaine and marijuana) and obesity. The group of patients (and the control group) underwent complementary tests such as lipid profile, blood biochemistry (glucose, urea, and creatinine), electrocardiogram, echocardiography, cerebral computerized tomography and/or MRI, coagulation profile, fibrinogen, D-dimer, lupus anticoagulant, and proteins C and S, to determine the aetiology of cerebral ischemia. Aetiology was classified following the criteria of the *Baltimore Washington Cooperative Young Stroke Study*,²⁵ adapted and validated for young adults (Table 2). The medical evaluation was carried out by a multidisciplinary unit consisting of specialists in Neurology, Internal Medicine, Cardiology, Endocrinology and Haematology. The information obtained was collected in a data collection instrument.

Regarding ethical aspects, informed consent was obtained from all patients and/or legal tutors, respecting their rights and guaranteeing the confidentiality of the information obtained, in accordance with the Helsinki Declaration.

Data processing and analysis

We used the statistical program SPSS 17.0 (evaluation version) for the statistical analysis.

We used hierarchical analysis in the selection of variables for multivariate analysis, which is based on a theoretical model that describes the hierarchical or parallel relation between two groups of risk factors relating to disease or health problems. These factors may not be the direct cause of the problem, so they are classified as distal determinants, and direct constraints as proximal determinants. Unlike other models, hierarchical analysis attempts to adapt the set of determinants considered distal by the proximal, mainly those related to lifestyles. This model also assumes that there are differences between factors, so it weighs the direct or indirect effect of each one on the problem being studied. The variables were grouped into blocks following a hierarchical model:

1. Block 1: Biological conditions
2. Block 2: Lifestyles
3. Block 3: Pathological conditions

Initially, both univariate and bivariate statistic analyses were carried out, and the variables deemed significant in the bivariate analysis were then entered into the multivariate analysis. A conditional logistic regression model was used to estimate the odds ratio (OR) and confidence intervals (CI) for this analysis. The variables from the first block that presented a positive association and statistical significance with ischemic CVD in the first stage continued to be part of the model in the later stages, except for the non-associated variables in the first 3 blocks. The final model was composed of variables selected from each stage of analysis, with their respective levels of statistical significance observed initially. The calculations were carried out with a confidence level of 95%.

Operational definitions

These are shown in Annex 1.

Results

A total of 30 patients with a first episode of ischemic CVD and 60 control patients were evaluated. The mean age for both groups was 36.80 ± 8.45 years and the distribution per gender showed that 53.3% were females and 46.7% were males. The mean age of males was 38.9 ± 5.7 years, while the mean age of females was 35.0 ± 10.1 ($P = .218$). Out of the total number of patients, 63.3% were recruited at the Hospital Nacional Dos de Mayo (Lima), 26.7% at the Hospital Daniel Alcides Carrión (Callao) and 10% at the Hospital Alberto Sabogal Sologuren (Callao).

The most frequent aetiologies using the *Baltimore-Washington Cooperative Young Stroke Study* classification were cardioembolism and atherosclerotic vascular disease, with 30% each (Table 3), whereas there were no cases of migrainous infarction.

When evaluating the possible risk factors for a first episode of cerebral ischemia, in comparison with control patients, it was found that the most common were valvular heart disease, obesity, smoking (Table 4) and HDL dyslipidemia. The multivariate analysis to determine independent risk factors that intervene in the first episode of CVD in young adults showed a statistically significant association with hypertriglyceridaemia, valvular heart disease and hormonal contraception/ replacement (Table 5).

Clinical characteristics of patients

Motor deficit (50%) and headaches (27%) were the most common form of presentation. Up to 40% of patients presented other complications during their stay at the hospital, with intracranial hypertension (25%) and acute pyelonephritis (16.8%) being the most frequent. Other complications included upper gastrointestinal bleeding, hypokalaemia, aspiration pneumonia, heart failure, hypoglycaemia, sepsis and hyperthermia (8.3% each). The mean length of stay at the hospital was 8.0 ± 2.9 days and the mortality rate was 10% (3 cases). Two thirds died due to intracranial hypertension and the other third due to urinary sepsis. During the monitoring period, one patient presented a second episode of cerebral ischemia.

Table 1 Aetiology of Ischemic cerebrovascular disease based on the *Baltimore Washington Cooperative Young Stroke Study* criteria

Aetiology	Criteria
Atherosclerotic vasculopathy	Ipsilateral intracranial or extracranial disease showing on an angiogram or a non-invasive test: Significant haemodynamic obstruction Obstruction > 60% Intraluminal clot plate Any detectable atherosclerotic disease
Non-atherosclerotic vasculopathy	Evidence of fibromuscular dysplasia, vasculitis, vascular dissection or other specific vasculopathy
Cardiac or transcardiac embolism	Demonstration of: Atrial fibrillation, atrial flutter Myocardial infarction, either recent (≤ 6 weeks before the cerebrovascular ischemic event) or remote (> 6 weeks), without any other abnormalities Akinetic or hypokinetic segment Cardiac thrombi Valvular vegetation or endocarditis Prosthetic heart valve Dilated cardiomyopathy Right-left shunt and/or accompanied by systemic or venous embolism (paradoxical embolism) Mitral valve prolapse without detectable clot Mitral calcification Aortic stenosis by calcification Other possible sources of embolism
Haematological/ others	Coagulation inhibitor deficiency, postpartum, autoimmune diseases (including antiphospholipid syndrome)
Lacunar infarction	One of the following: Infarction < 15 mm in the territory of deep perforators compatible with sensorimotor, pure motor or pure sensory deficits, ataxic hemiparesis or dysarthria Normal brain imaging study or non-specific lesion size, pure motor or pure sensory deficit, ataxic hemiparesis or dysarthria (excluding sensorimotor deficit)
Migrainous infarction	At least 1 attack of migraine with persistent neurological deficit for more than 24 hours and/or evidence of cerebral ischemia through magnetic resonance or computed tomography; as well as: Previous history of common, classic or complicated migraine Typical migraine headache Absence of other risk factors for cerebral ischemia
Related to the use of oral contraceptives or exogenous oestrogen	Use, in the 3 months prior to study, of: Oral contraceptives Hormone replacement therapy
Related to illicit drugs	Report of illicit drug use within 48 hours prior to ischemic cerebral event and/or positive toxicology screening
Indeterminate	When none of the mentioned diagnostic criteria are met

Discussion

Cerebral ischemia is an important cause of mortality and disability in South America due to recent lifestyle changes and increased life expectancy of the population. Some studies show that its onset in young adults is increasing and

that an age lower than 45 is a predictor of ischemic episodes with unusual causes, although with better prognosis.³⁰

There have been some state-wide studies carried out in cities of Bolivia, Colombia, Chile, Ecuador and Peru that show an incidence rate of 0.35 to 1.83 annual cases per 1,000 inhabitants.^{3,31} However, these studies have not

Table 2 Aetiologies of a first episode of cerebral ischemia in young adults from 3 hospitals in the city of Lima, based on the *Baltimore-Washington Cooperative Young Stroke Study* classification

Aetiology	Frequency	Percentage
Atherosclerotic vasculopathy	09	30.0%
Cardiac/ transcatheter embolism	09	30.0%
Indeterminate	05	16.7%
Haematological or others	02	6.6%
Related to hormonal contraception/ replacement	02	6.6%
Non-atherosclerotic vasculopathy	01	3.3%
Lacunar stroke	01	3.3%
Related to illicit drug consumption	01	3.3%

Table 3 Possible risk factors for a first episode of cerebral ischemia in young adults from 3 hospitals in Lima and Callao and clinically healthy controls

Factor evaluated	Frequency of ischemic cerebrovascular disease group	Percentage	Frequency of control group	Percentage
Valvular heart disease	09	36.6%	01	1.6%
HDL dyslipidemia	09	30.0%	14	23.3%
Obesity	08	26.6%	00	0%
Smoking	08	26.6%	01	1.6%
Chronic alcoholism	07	23.3%	00	0%
Consumption of cocaine	06	20.0%	00	0%
Hormonal contraception/ replacement	06	20.0%	02	3.3%
Hypertriglyceridaemia	05	16.6%	02	3.3%
Arterial hypertension	05	16.6%	02	3.3%
Consumption of marijuana	05	16.6%	00	0%
LDL dyslipidemia	04	13.3%	02	3.3%
Migraine	04	13.3%	02	3.3%
Diabetes mellitus	03	10.0%	00	0%
Acute alcohol intake	02	6.6%	00	0%
Tuberculous meningoencephalitis	02	6.6%	00	0%

Table 4 Multivariate analysis with conditional logistic regression of possible risk factors for a first episode of cerebral ischemia in young adults from 3 hospitals in Lima and Callao

Variables		Block 1: biological factors	Block 2: lifestyles	Block 3: pathological conditions
	PValue	Adjusted OR (95%CI) ^a	Adjusted OR (95%CI) ^b	Adjusted OR (95%CI) ^c
Obesity	NS	NS	—	—
Hormonal contraception/ replacement	0.002	—	28.38 (3.49-231.03)	—
Hypertriglyceridaemia	0.014	—	33.15 (2.04-538.78)	—
Smoking	NS	—	NS	—
Consumption of illicit drugs	NS	—	NS	—
Valvular heart disease	0.001	—	—	61.13 (5.26-710.37)

^aAdjusted odds ratio (OR) for the variables: hormonal contraception/ replacement, hypertriglyceridaemia, smoking, consumption of illicit drugs and valvular heart disease.

^bAdjusted OR for the variables: obesity and valvular heart disease.

^cAdjusted OR for the variables: obesity, hormonal contraception/ replacement, hypertriglyceridaemia, smoking and consumption of illicit drug.

CI: confidence interval; NS: not significant.

provided new information about incidence, aetiology and risk factors in young adults. Studies carried out in hospitals are rare or are performed on a general level without mentioning young adults.^{11,32}

The present study shows that hypertriglyceridaemia, valvular heart disease and hormonal contraception/replacement were risk factors for a first episode of cerebral ischemia in young adults from 3 hospitals in Lima and Callao, while cardioembolism and atherosclerotic vascular disease were the most frequent aetiologies.

There is a certain amount of controversy about the role of dyslipidemia as a risk factor for cerebral ischemia.^{22,33-37} Our study shows that hypertriglyceridaemia alone is a risk factor, in accordance with the findings of Lindenstrom et al.³³ who concluded that a high level of triglycerides in plasma was associated with a risk of ischemic CVD. Olmos¹⁸ and Nightingale³⁸ reported that valvular heart disease was a risk factor for cerebral ischemic vascular disorders, in which cardiac embolism was the mechanism; however, their study groups consisted of only females. In our findings, valvular heart disease proved to be a risk factor, which allows us to highlight the importance of studying cardiovascular diseases in this group of patients even when they do not present clinical manifestations. The findings reported about the role of hormonal contraceptives (mostly oral contraceptives) and hormone replacement therapy as risk factors for venous thromboembolism have also been confirmed.³⁹⁻⁴²

Our results in young adults in the 3 hospitals studied are similar to those described by Vera¹¹ in the Hospital EsSalud Guillermo Almenara Irigoyen (Lima, Peru), which also stated that one of the most frequent aetiologies was cardioembolism, classified following the indications of the *Baltimore-Washington Cooperative Young Stroke Study*. It should be noted that we found a smaller percentage of aetiologies of unknown cause (17%) compared to the 28.6% found in the study mentioned previously. A case of non-atherosclerotic vascular disease of infectious origin associated to HIV and syphilis was found at one of the participating hospitals. This case was implicated in the development of ischemic CVD, which matches reports from international medical literature.^{43,44}

Regarding observations in patients, the prognosis in young adults with a first episode of cerebral ischemia is good in terms of mortality (10%), recurrence (3.3%) and length of hospital stay (8.0±29 days); it is important to highlight that infectious complications are frequent (acute pyelonephritis, aspiration pneumonia and sepsis), although they are easy to handle with adequate medical management. Many studies include transient ischemic episodes; we have excluded these patients because transient focal signs in this age group are not generally caused by vascular diseases, but rather by other disorders such as migraines and multiple sclerosis.

One limitation of this study is the size of the sample, which has influenced the confidence intervals of our estimations; however, this does not interfere with the associations observed for risk factors in our sample. Despite this, potential confusion factors have been controlled through selection criteria, pairing techniques and hierarchical multivariate analysis, so we believe that the results obtained are valid.

Annex 1. Operational definitions used in the study

Variable	Operational definition
Cerebrovascular disease	Clinical signs of focal disorders of brain function, which develop rapidly, with symptoms lasting more than 24 hours or leading to death without any other apparent cause besides vascular origin
Cerebral ischemia	Set of clinical, radiological and imaging manifestations that appear as a result of qualitative or quantitative alteration of circulatory flow to a brain area, determining a neurological deficit with duration of over 24 hours
Arterial hypertension ²⁶	In accordance with the <i>Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure</i> (JNC 7): systolic blood pressure higher than 140mmHg or diastolic blood pressure higher than 90mmHg
Diabetes mellitus (DM) ²⁷	According to the classification of the World Health Organization and the American Diabetes Association (2003): presence of classic symptoms of diabetes (polyuria, polydipsia, unexplained weight loss) plus blood glucose values occasionally above 200mg/ dl; fasting glucose higher than 126mg/ dl; glucose tolerance test 2 hours after a 75g glucose load higher than 200mg/ dl. Diagnosis by an endocrinologist and/ or resident physician
Valvular heart disease	Diagnosis of valvular heart disease prior to the ischemic episode or during the study with cardiology tests (electrocardiogram and echocardiography)
Smoking	Smoking at least 1 cigarette per day for at least 3 months before the cerebral ischemic event
Contraception/ hormone replacement	Use of oral contraceptives or hormone replacement therapy for at least 6 months prior to the ischemic episode
Alcoholism	Previous intake >60g/ day of alcohol during the previous 2 months
Dyslipidemias ²⁸	We used the LDL and HDL cut-off values established as appropriate according to the <i>Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults</i> (ATP III): LDL below 130mg/ dl, HDL higher than 40mg/ dl in men and higher than 50mg/ dl in women; patients with LDL value above and HDL values below those mentioned according to gender were classified as dyslipidemic patients

Annex 1 (Continued)

Variable	Operational definition
Migraines ²⁹	According to the criteria of the <i>International Classification of Headache Disorders</i> , 2nd ed (ICHD-II)

Concluding, hypertriglyceridaemia, valvular heart disease, smoking and hormonal contraception/ replacement were independent risk factors for a first episode of cerebral ischemia in young adults at 3 hospitals in Lima and Callao, with the most frequent aetiologies being cardioembolism and atherosclerotic vascular disease.

Conflict of interest

This study was financed by the Medicine School of the Universidad Nacional Mayor de San Marcos through the Research Unit, which had no influence on the design of the study, the collection, analysis and interpretation of data, or in the preparation, review and approval of this work. This study has not been presented at any medical conferences.

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