


# Pediatric Arterial Ischemic Stroke: Clinical Presentation, Risk Factors, and Pediatric NIH Stroke Scale in a Series of Chilean Patients

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## Abstract

Stroke is an important cause of morbidity and mortality in children. Clinical presentation is diverse, and multiple risk factors have been described. The aim of this retrospective study is to describe the clinical presentation, risk factors, and the Pediatric National Institute of Health Stroke Scale (PedNIHSS) in a series of pediatric Chilean patients with the diagnosis of arterial ischemic stroke (AIS). Children diagnosed with AIS aged between 29 d and 18 y were enrolled (1989 to 2016). Clinical characteristics and risk factors were described. PedNIHSS severity score was estimated for patients older than 4 mo of age. Sixty-two patients were included, 66% were male, and the mean age of presentation was 3.5 y. Seventy-nine percent presented motor deficit, 45% seizures, and 15% consciousness impairment. Eighty-two percent had a unilateral stroke and 73% had anterior circulation territory affected. The main risk factors were arteriopathy (63%) and infection (43%). The PedNIHSS mean was 7.6, ranging between 0 and 17. In the categories in which it was possible to apply  $\chi^2$  test, only the acute systemic conditions category was statistically significant ( $P = 0.03$ ), being higher in the group of patients younger than 3 y old. We confirmed male predominance in AIS and the most frequent presenting symptom was motor deficit. We found at least 1 risk factor in all patients with complete information. We confirmed arteriopathy as the most frequent risk factor, and acute systemic conditions were higher in patients younger than 3 y old with statistical significance ( $P = 0.03$ ). The majority of patients presented mild to moderate severity in the PedNIHSS score.

## Keywords

arterial ischemic stroke, pediatric stroke, risk factor, PedNIHSS

## Introduction

Stroke and cerebrovascular disorders are an important cause of morbidity and mortality in children, being among the top 10 causes of childhood death and probably increasing in prevalence. Recent epidemiological data suggest incidence rates between 2 and 13/100,000 children/year for childhood stroke<sup>1-3</sup>. The incidence may have increased over the last 25 y because of increased recognition, less invasive vascular diagnosis, and therapeutic advances, allowing children with predisposing conditions to survive<sup>1</sup>. There is a significant prehospital and in-hospital delay in pediatric stroke<sup>4</sup> because of the existing low clinical suspicion and the variety of stroke mimics during childhood<sup>2</sup>.

Pediatric arterial ischemic stroke (AIS) appears to have a significant male predominance for reasons that are not well understood. African American children have a higher risk of stroke even after accounting for sickle cell anemia<sup>1-3,5,6</sup>.

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Clinical presentation includes focal (82%) or diffuse (64%) neurological signs<sup>7</sup>. Diffuse neurological signs are more common in patients presenting acute systemic conditions and focal signs are more common in patients with arteriopathies, cardiac anomalies, chronic systemic infections, or prothrombotic states. Children younger than 1 y old present mainly with seizures or impairment of consciousness, and older children develop focal neurological signs more frequently<sup>7,8</sup>. The Pediatric National Institute of Health Stroke Scale (PedNIHSS) is a quantitative score that measures the neurological deficit related to the ischemic event that was adapted from adult NIHSS and has been demonstrated to have an excellent interrater reliability<sup>9,10</sup>.

Chile has a dual health-care system under which its citizens can voluntarily opt for coverage by either the public National Health Insurance Fund (Fondo Nacional de Salud [FONASA] in Spanish) or any of the country's private health insurance companies. Currently, 68% of the population is covered by the public fund and 18% by private companies<sup>11</sup>. San Borja Arriarán Hospital is part of the public health system and oversees specific areas of Santiago, Chile. However, its pediatric neurology department acts as a national referral center for complex neurology patients from all over the country.

The aim of this study is to describe the clinical presentation, risk factors, neuroimages, and PedNIHSS of a group of Chilean pediatric patients with pediatric AIS.

## Materials and Methods

### Study Design

Children aged between 29 d and 18 y diagnosed with AIS were enrolled in a clinical database maintained along the study period. They were all diagnosed or referred to the Pediatric Neurology Department of San Borja Arriarán Hospital, Santiago, Chile, between 1989 and 2016. Clinical records were retrospectively reviewed.

Clinical characteristics and risk factors were described for the whole sample and sorted by age-group. Information relative to risk factors was categorized according to predetermined definitions of the International Pediatric Stroke Study (IPSS)<sup>7</sup>. PedNIHSS was estimated for patients older than 4 mo.

Stroke-like episodes, nonarterial strokes, sinovenous thrombosis, ischemic events without infarction, hemorrhagic strokes, diffuse hypoxic brain damage, and perinatal or presumed perinatal strokes were excluded.

### Analysis

A clinical profile of the series of cases was described, including age at the time of stroke, gender, presenting symptoms, and lesion location. The risk factors were clustered in 10 different categories: arteriopathy, infection, prothrombotic states, risk factors for atherosclerosis, cardiac disorders, acute systemic conditions, acute head and neck disorders, chronic systemic conditions, chronic head and

neck disorders, and others<sup>7</sup>. The analysis done for calculating the prevalence (%) of the risk factors is explained below.

The risk factor's prevalence was calculated for each category. Because of the lack of evaluations for each of the 10 categories (not all the patients were studied in every category), the risk factor's prevalence was calculated with a different total number of patients. The total number of patients were the cases studied for each category. The risk factor prevalence was calculated with the patients who were evaluated and had the risk factor present over the total number of patients who were studied in that category. Different risk factor categories were not mutually exclusive, so each patient was included in different categories if multiple risk factors existed. Because children may have more than 1 specific risk factor present in each category, the sum of specific risk factors was higher than the total<sup>7</sup>. For each risk factor category, patients were sorted by age-group: <3 y old and  $\geq 3$  y old. This cutoff based on age was selected because of the statistical differences we found in the risk factors. Then,  $\chi^2$  test was applied looking for a statistic difference in the risk factors according to the age of the patients. The  $\chi^2$  test was applied only in the categories that had  $\geq 4$  patients studied.

For patients, older than 4 mo, the PedNIHSS severity score was calculated reviewing clinical records<sup>9,10,12</sup>. Score was assessed by a pediatric neurologist based on pediatrician description at the time of arrival to the emergency room (ER) in hospital. A pediatric neurologist reviewed the clinical records of the patients of the ER, and consigned each item of the PedNIHSS, and then the final score was retrospectively calculated<sup>10</sup>.

## Results

### Population Characteristics

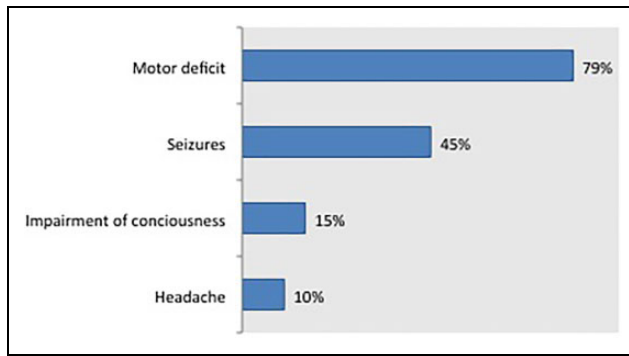
A total of 62 patients were included in the study, 41 (66%) were male and 21 (34%) were female. The mean age at onset was 3.55 y and the median was 2.79 y old, with a minimum of 0.08 y and a maximum of 14.02 y. The result did not follow a Gaussian distribution.

### Initial Symptoms

Forty-nine patients (79%) presented hemiparesis or motor involvement, 28 (45%) cases epileptic seizures, 9 (15%) presented consciousness involvement, and 6 patients (10%) had headache (Fig. 1).

### Topography of the Ischemic Lesion

The topography was determined in all patients through neuroimaging (Computed tomography scan [CT] and/or magnetic resonance [MR] imaging). Fifty-seven patients (92%) had a cerebral CT done, 49 patients (79%) had a cerebral MR done, and 45 patients (73%) had both neuroimaging done. Only half



**Fig. 1.** Most of the patients presented with motor involvement (79%) and seizures (45%). Patients presented less frequently with consciousness impairment (15%) and headache (10%).

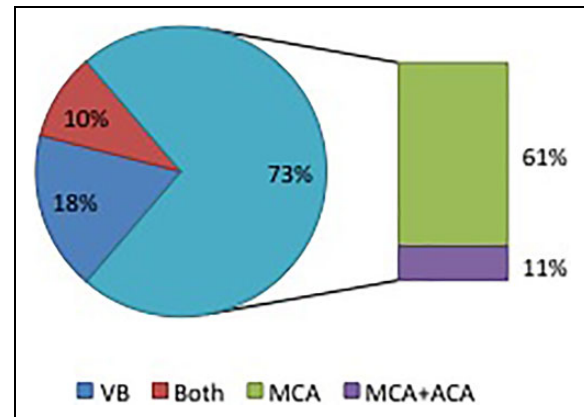
of our cases had a vascular study done (angiography CT, angiography MR, or conventional angiography). In 45 cases (73%), the ischemic parenchymal involvement was in the anterior cerebral circulation, 38 (61%) of these patients had the middle cerebral artery compromised and 7 patients (11%) had both the middle and anterior cerebral arteries involved. In these series, none of the cases had involvement of the anterior cerebral artery territory exclusively. The territory irrigated by the posterior circulation was compromised in only 11 patients (18%), and 6 cases (10%) had both anterior and posterior circulation affected (Fig. 2). Four patients (6%) presented a hemorrhagic component in the neuroimaging. In 11 cases (18%), there was a bilateral involvement of the cerebral parenchyma.

### Risk Factors

Only 15 patients (24.2%) had a complete evaluation of all 10 categories of risk factors. In the other 47 (75.8%) cases, the information was incomplete: there were no data in at least 1 category of risk factors (because the study was not performed completely; Table 1).

The most frequent risk factor was arteriopathy 20/32 (63%). This means that 32 patients were studied for arteriopathy and of the 32 patients, 20 had an abnormal exam. This was followed by infection 23/54 (43%), prothrombotic states 13/37 (35%), risk factors for arteriosclerosis in adulthood 9/39 (23%), acute systemic conditions 16/62 (26%), cardiac disorders 10/45 (22%), acute head and neck disorders 10/62 (16%), chronic systemic conditions 5/62 (8%), and chronic head and neck disorders 3/62 (5%). Other risk factors, not classifiable in the categories mentioned above, were present in 7/62 (11%) patients (Table 1). Regarding the 15 patients with complete study in all the categories, risk factors were found in at least 1 category in all cases and 13 presented risk factors in 2 or more categories.

We compared the prevalence of risk factors in each category for each age group (<3 or ≥3 y old; Table 2). The most frequent risk factor (arteriopathy) was higher in patients older than 3 y, but the difference was not statistically significant between the 2 groups. The prevalence of acute head and neck disorders and risk factors for adult arteriosclerosis



**Fig. 2.** Topography of the ischemic lesions. The most frequently compromised territory was the anterior circulation (73%), being the MCA territory the most frequently affected territory; 18% of the patients presented compromise of the posterior circulatory territory and only a 10% had an ischemic lesion in both territories. VB = vertebrobasilar territory; both = anterior and posterior circulation territories; MCA = middle cerebral artery; ACA = anterior cerebral artery.

was higher in patients older than 3 y. The prevalence of chronic systemic conditions, and chronic head and neck disorders, was higher in patients younger than 3 y. In the categories that it was possible to apply  $\chi^2$  test, only the acute systemic conditions category was statistically significant ( $P = 0.03$ ), being higher in the group of patients younger than 3 y old (Table 2).

### PedNIHSS Severity Scale

An average score of 7.6 was obtained, with a maximum of 17 and a minimum of 0 points when PedNIHSS severity scale was calculated from the clinical records for patients older than 4 mo (56 patients; Table 3). When the severity score of the categories was stratified (extrapolated from the adult NIHSS scale)<sup>13</sup>, 2 patients (4%) were found to have a score equal to 0 (no stroke), 12 (21%) patients with score between 0 and 2 (mild), 39 (70%) patients between 5 and 15 (moderate), and 3 (5%) patients between 15 and 20 points (moderate to severe). There were no cases with scores that corresponded to severe vascular accident (between 21 and 42; Table 3).

### Discussion

The group of patients studied had a male predominance as previously described in the literature. In adults, there is a clear predominance of males under 80 y old in AIS. Several reports have reported this prevalence in children<sup>1-3,5,6</sup>. A multicenter IPSS study found a clear male predominance that persisted after stratification by age-group, type of vascular accident or history of trauma<sup>5</sup>.

The most important initial symptoms were motor deficit and seizures. The IPSS study, similarly, found a frequency of focal signs of 82%, diffuse signs in 64%, and epileptic

**Table I.** Risk Factors Prevalence.

RF Category	NP Studied (NP)	NP with a Positive RF	Subcategory	Positive RF (RF+)	RF+/NP (%)	RF Prevalence (%)
Arteriopathy	<b>32</b>	<b>20</b>	Unspecified	<b>8</b>	<b>25</b>	<b>63</b>
			Arterial dissection	5	16	
			Moyamoya	4	13	
			Post varicella	2	6	
			Vasculitis	1	3	
Infection	<b>54</b>	<b>23</b>	Sickle cell anemia	0	0	<b>43</b>
			Varicella	<b>6</b>	<b>11</b>	
			Respiratory infection	4	7	
			Chlamydia	2	4	
			<i>Escherichia coli</i>	2	4	
			Mycoplasma	2	4	
			Otitis	2	4	
			Herpes simplex	1	2	
			<i>Streptococcus pneumoniae</i>	1	2	
			Typhoid	1	2	
			Urinary tract infection	1	2	
			Unknown	1	2	
			Prothrombotic states <sup>a</sup>	<b>37</b>	<b>13</b>	
Antithrombin III deficit	2	5				
Factor V Leiden	2	5				
Protein C deficit	2	5				
Protein S deficit	1	3				
Lupus anticoagulant antibodies	1	3				
Elevated Lp(a)	1	3				
RF for atherosclerosis	<b>39</b>	<b>9</b>	Hyperlipidemia	<b>9</b>	<b>23</b>	<b>23</b>
Acute systemic conditions <sup>a</sup>	<b>62</b>	<b>16</b>	Fever	<b>15</b>	<b>24</b>	<b>26</b>
			Sepsis	2	3	
			Dehydration	1	2	
			Arterial hypertension	1	2	
Cardiac disorders <sup>a</sup>	<b>45</b>	<b>10</b>	Anoxia	1	2	<b>22</b>
			Congenital heart disease	<b>3</b>	<b>7</b>	
			Arrhythmias	2	4	
			PFO	2	4	
			Left ventricular hypertrophy	2	4	
Acute head and neck disorders	<b>62</b>	<b>10</b>	Dilated cardiomyopathy	1	2	<b>16</b>
			Myocarditis	1	2	
			Meningoencephalitis	<b>3</b>	<b>5</b>	
			Trauma	3	5	
Chronic systemic conditions	<b>62</b>	<b>5</b>	Otomastoiditis	2	3	<b>8</b>
			Meningitis	1	2	
			Sinusitis	1	2	
			Anemia	<b>2</b>	<b>3</b>	
			Arterial hypertension	1	2	
Chronic head and neck disorders	<b>62</b>	<b>3</b>	Hypothyroidism	1	2	<b>5</b>
			Genetic diseases	1	2	
			Intracranial arteriovenous malformation (AVM)	<b>2</b>	<b>3</b>	
			Venous angioma	1	2	
Others <sup>a</sup>	<b>62</b>	<b>7</b>	Acute renal failure	1	2	<b>11</b>
			Chronic renal failure	1	2	
			Behçet's disease	1	2	
			Celiac disease	1	2	
			Connective tissue disease	1	2	
			Goodpasture disease	1	2	
			Hemolytic uremic syndrome	1	2	
			Idiopathic thrombocytopenic purpura	1	2	
			Schönlein-Henoch disease	1	2	

Note: In each category, the most frequent risk factor is highlighted in boldface. The most frequent RF were arteriopathy (63%), infection (43%), and prothrombotic states (35%). PFO = patent foramen ovale; RF = risk factors; NP = number of patients.

<sup>a</sup>In these categories, 1 patient had more than 1 risk factor in the subcategories.

**Table 2.** Risk Factors Category Prevalence Sorted by Age-group ( $\chi^2$  Test,  $P < 0.05$ ).

Risk Factor Category	<3 Y	$\geq 3$ Y	P
Arteriopathy	6/13 (46%)	14/19 (74%)	0.1141
Cardiac disorders	4/23 (17%)	5/22 (23%)	0.6546
Chronic systemic conditions	3/32 (9%)	2/30 (7%)	<sup>a</sup>
Prothrombotic states	6/19 (32%)	6/17 (35%)	0.1452
Acute systemic conditions	12/32 (28%)	4/30 (13%)	0.03
Chronic head and neck disorders	2/32 (6%)	1/30 (3%)	<sup>a</sup>
Acute head and neck disorders	8/32 (25%)	2/30 (40%)	<sup>a</sup>
Infections	11/30 (37%)	12/24 (42%)	0.3248
Risk factors for atherosclerosis	2/19 (11%)	7/20 (35%)	<sup>a</sup>
Others	1/32 (3%)	6/30 (20%)	<sup>a</sup>

Note: In the categories in which it was possible to apply  $\chi^2$  test, only the acute systemic conditions category was statistically significant ( $P = 0.03$ ), being higher in the group of patients younger than 3 y old.

<sup>a</sup>In these categories,  $\chi^2$  test could not be applied because the number of patients was lower than 4.

**Table 3.** Retrospective PedNIHSS Score Calculated in Patients Older than 4 Mo.

PedNIHSS Score	PedNIHSS Category	Percentage		
		n	(%)	
Average	7.6	No stroke (0)	2	4
Min	0	Mild (1 to 4)	12	21
Max	17	Moderate (5 to 15)	39	70
		Moderate to severe (15 to 20)	3	5
		Severe (21 to 42)	0	0
		Total	56	

Note: Most of the patients had a moderated severity (70% had a score between 5 and 15 points). n = number of patients; min = minimum; max = maximum; PedNIHSS = Pediatric National Institute of Health Stroke Scale.

seizures in 31%<sup>10</sup>. In other international studies, acute hemiparesis is also the most frequent form of presentation in up to 94% of cases<sup>14-16</sup>. Seizures are present in 20% to 48% of cases<sup>16</sup>. There is some variability in the frequency of focal, diffuse, and epileptic symptomatology in the different reports.

Younger children tend to present encephalopathy, impaired consciousness, apneas, and seizures, without focal signs more frequently<sup>3,16</sup>; however, a detailed neurological examination will usually also identify focal deficit<sup>2</sup>. Headache and language impairment are difficult to recognize in children younger than 1 y because of their lower expressive capacity<sup>3</sup>. In a study published in 2007, it was recognized that children younger than 1 y were more likely to have seizures (45.5% vs. 10.8%) and mental status disturbances (36.4% vs. 7.7%) with a lower probability of having focality (45.5% vs. 76.9%) than those older than 1 y<sup>8</sup>.

The analysis performed in our population with AIS revealed a high prevalence of risk factors. In all patients in whom it was possible to perform the study of risk factors completely, there was at least 1 risk factor in all cases,

revealing a good performance of the analysis. The main risk factor was arteriopathy (63%) as reported in several international studies<sup>7</sup>. This result could be higher considering that not all patients had vascular images and, which due to low resources, was only performed in patients in whom arteriopathy was clinically suspected. No patient was diagnosed with transient cerebral arteriopathy, although in previous works it has been described as the most frequent arteriopathy subtype<sup>7</sup>. This can be explained by a bias due to the lack of availability to perform a follow-up vascular image 6 mo after AIS, which is necessary for the diagnosis of transient focal arteriopathy, to prove stability or improvement. Thus, patients with focal stenosis could only be classified as unspecified arteriopathy. Prevalence of infections and prothrombotic states were found to be higher in our patients than previously described.

There is a lower frequency of heart disease in our patients compared to international studies (22% vs. 31%, respectively)<sup>7</sup>. In Latin American countries, there is a lower survival of cardiac patients, making the occurrence of heart disease complications, such as stroke, less likely. On the other hand, the proportion of children with echocardiographic study in our series is lower than in other studies, probably responding to less access to such exams, especially in past decades.

Although, not statistically significant, the prevalence of arteriopathy was higher in patients older than 3 y, as reported in previous studies, where the highest prevalence has been found between 5 and 9 y of age, with age being a predictor of arteriopathy. Acute systemic conditions are more prevalent in younger patients as described in international studies<sup>7</sup>.

Multicenter studies have not been able to establish causality of the so-called risk factors due to the lack of studies with control groups. To determine if conditions identified as risk factors, which are common in pediatric patients, have a causal role, it will be necessary to perform a cases and controls study. A study of this nature was published in 2012 and identified as independent risk factors: The history of trauma 12 wk prior to vascular accident (12% of cases vs. 1.6% of controls, Odds ratio [OR] = 7.5) and the presence of minor infection the previous month (33% of the cases vs. 13% of the controls, OR = 4.6)<sup>17</sup>.

Regarding PedNIHSS severity scale, it was found that most patients presented mild to moderate clinical severity, with an average score of 7.6. A study published in 2012 with 75 patients found similar results, with 7.6 points on average when applying the PedNIHSS in a retrospective way from the clinical records<sup>10</sup>.

This study has several limitations. First, it is a retrospective study, therefore, there can be bias in the recompilation of data because of record error or lack of data. Second, the period of study was very large, 27 y in total (from 1989 to 2016), in which there have been many advances in studies and more precise and available neuroimaging, being very different from 1989 until now. Third, unfortunately, not all the patients had a complete risk factor study done because of the lack of resources and because many patients are from the

countryside and rural areas, we are unable to access many studies. Fourth, many studies, laboratory exams and vascular images, were requested according to the clinical symptoms, not by a stroke protocol. Finally, most of our patients do not have follow-up neuroimaging, therefore, we weren't able to determine if focal arteriopathy evolved as transient arteriopathy, so they remained classified as unspecified arteriopathy.

## Conclusions

This study provides information on the clinical characteristics and risk factors of a considerable number of patients in a Chilean national referral center.

We confirmed male predominance and motor deficit at debut as previously described. The territory irrigated by the middle cerebral artery is frequently the most affected. We found at least 1 risk factor in all patients with complete information. We confirmed arteriopathy as the main risk factor, but we did not find any case of focal transient arteriopathy; this may be because of lack of follow-up neuroimaging. The initial severity of the AIS estimated with PedNIHSS is mostly mild to moderate.

## Ethical Approval

This study was approved by our institutional review board.

## Statement of Informed Consent

Statement of Informed Consent was obtained verbally or written from legally authorized representatives.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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