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Clinical and radiological risk factors for poststroke epilepsy in childhood

Mauricio López-Espejo [a,*], Marta Hernández-Chávez [a], Isidro Huete [b]

[a] Unit of Neurology, Division of Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile
[b] Department of Radiology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

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ABSTRACT

Background: There are few studies evaluating risk factors for poststroke epilepsy (PSE) after an arterial ischemic stroke (AIS) in childhood. This study aimed to evaluate clinical and radiological predictors for PSE in a cohort of children with a first-ever AIS.
Methods: A retrospective analysis of a single-center prospective consecutive cohort of children beyond neonatal age with a first-ever AIS admitted at the Pontifical Catholic University of Chile's Clinical Hospital between 2003 and 2013. All participants had a brain magnetic resonance imaging at the time of diagnosis. All children underwent follow-up for at least three years with an annual clinical evaluation. We used the current epilepsy definition of the International League Against Epilepsy. Studied variables include demographics, clinical manifestations at onset, stroke risk factors, and radiological characteristics of AIS. Cox proportional hazards regression analysis was used to evaluate PSE risk adjusted for clinical and radiological variables.
Results: Among 98 children who met the study criteria, 41 (41.8%) with PSE. Following multivariate analysis, it was determined that the predictors of PSE include young age at AIS (hazard ratio [HR] = 0.91; confidence interval [CI] = 0.84–0.99), the occurrence of acute symptomatic seizures (HR = 3.29; CI = 1.35–8.01), cortical infarction (HR = 5.01; CI = 2.00–12.6), and multifocal infarction (HR = 3.27; CI = 1.01–10.8).
Conclusion: Seizures, young age, cortical lesions, and multiple infarction at the time of stroke are independent risk factors for PSE in children following a first-ever AIS.

1. Introduction

The annual arterial ischemic stroke (AIS) incidence rate ranges from 1.2 to 7.9 per 100,000 children beyond the first month of life [1,2]. Although AIS has a rather low incidence in children compared with adults, the risk to develop epilepsy is higher in this age group [3–5]. Previous studies have reported several risk factors for poststroke epilepsy (PSE) in childhood, including the occurrence of acute symptomatic seizures (AS) at the time of diagnosis, young age at onset of AIS (notably in infancy), and cortical involvement [5–7]. Also, there are numerous probable associated variables, such as involvement of the middle cerebral artery (MCA) territory and the presence of focal cerebral arteriopathy [3,8]. Although both cortical involvement and younger age at the time of AIS are strongly associated with a higher likelihood of AS, there are still no prospective studies evaluating the interrelation of these variables and the individual effect of these factors on the probability of developing PSE in childhood. Therefore, our aim in the current study was to evaluate the individual effect of aforementioned risk factors for PSE in a cohort of children with a first-ever AIS. We hypothesized that there are both clinical and radiological independent risk factors for PSE, which can be used to identify high-risk children after an AIS.

2. Materials and methods

We conducted a retrospective analysis of a single-center prospective consecutive cohort at the Pontifical Catholic University of Chile's Clinical Hospital. All clinical, laboratory, and radiological information was entered into a database, corrected according to a review of medical and neuroimaging records, and enrolled according to the institutional protocols [9]. We included all children aged 29 days to 18 years with radiologically confirmed AIS (defined as acute neurological symptoms or signs secondary to acute focal cerebral infarction in an arterial distribution on magnetic resonance images [MRIs]) occurring between January 2003 and July 2013. We exclude patients with previous epilepsy, suspected perinatal stroke, previous childhood AIS, moderate to severe hypoxic–ischemic encephalopathy, cerebral sinovenous and veins thrombosis, intracranial hemorrhage (not attributable to hemorrhagic transformation of AIS), prematurity (less than 37 weeks of gestation at birth), cranial surgery, intracranial tumor-related stroke,

* Corresponding author at: Unit of Neurology, Division of Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Diagonal Paraguay 362, Santiago 8330077, Chile.
E-mail address: mlopeze@med.puc.cl (M. López-Espejo).

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and moderate to severe traumatic brain injuries. The institution's ethics committee approved this study.

A pediatric neurologist obtained imaging and clinical data of acute event during the hospital stay. Demographics (age and sex), clinical manifestations (decreased level of consciousness, defined as Glasgow Coma Score < 12 points; headache in the prior 12 h; AS (defined as any clinical seizure occurring within 7 days of IIA [10]), and focal neurological deficits including motor, visual, or language impairment), underlying conditions (according to the International Pediatric Stroke Study [11]), and radiological stroke characteristics (infarct location, cerebral lobe involved, arterial territory involved, infarct number, and infarct laterality) were analyzed. Sixty-three children had vascular imaging (56 by magnetic resonance angiography). A radiologist evaluated all MRI sequences (diffusion-weighted image, fluid-attenuated inversion recovery, double inversion recovery, and T1 with gadolinium, using 1.5 T with 5-mm-thick slices, and 2.5 mm separation between cuts) and posteriorly were reviewed by two physicians (an experienced neuroradiologist and a pediatric neurologist) together. A pediatric neurologist obtained late seizures and electrophysiology data during at least an annual outpatient appointment or a home visit. Any documented unprovoked seizure that occurred after 1 week of IIA onset was encoded as a late seizure. All children with a late seizure had a standard interictal electroencephalogram (international system 10/20 and activated with hyperventilation and photostimulation) performed within the first two weeks after the seizure. PSE was defined by the occurrence of at least 2 unprovoked seizures occurring >24 h apart within 2 years after the stroke [12].

All statistical analyses were conducted using the IBM SPSS Statistics version 20 (IBM Corp., Somers, NY) software. The clinical presentation, radiological characteristics, sex, and categories of AIS Risk Factors (RFs) were expressed as both absolute and relative frequencies, and the age of onset and the follow-up period, as either means or medians and ranges, as appropriate. Cox proportional hazards regression analysis were used to estimate individual risk. Variables with $P < 0.05$ in the univariate regression analysis were subjected to a multivariate analysis in which we used the log-rank to compare Cox proportional hazard ratios (HRs) and evaluate relative risk. A 2-sided P value <0.05 was regarded as statistically significant.

3. Results

Among 107 patients, who had met the study criteria, 9 (8.4%) were lost or declined to participate. The study group consisted of 98 patients who suffer a first AIS in childhood, including 41 children (41.8%) who developed PSE and 57 children (58.2%) without PSE. Demographic, underlying conditions and stroke characteristics are summarized in Table 1. The median age of the children at the time of diagnosis was 2.16 years (interquartile range, 0.42–7.82). Time of the follow-up ranged from 0.12 to 8.49 years (mean, 3.92; standard deviation, 2.12).

Among 41 patients with PSE, 28 (68.3%) were diagnosed during the first year after AIS, 8 (19.5%) at the second year, 4 (9.8%) at the third year, and 1 (2.4%) at the fourth year of follow-up. All children with PSE were treated with antiseizure medication (ASM). Thirty-one children (75.5%) had been treated with 1 ASM, 7 (17.1%) with 2 ASMs, and 3 (7.4%) with 3 ASMs. Despite the ASM number, six children (14.6%) presented at least one seizure a month.

At least 1 AIS risk factor was documented in 90 (91.8%) children, and nearly half (56.2%) had multiple risk factors. The most common detected underlying conditions were acute infections, heart diseases, and other chronic conditions, which account for 38.8%, 37.8%, and 32.7% of the study cohort, respectively. By contrast, central nervous system (CNS) arteriopathies are relatively uncommon. These are documented in one-third of children who underwent a brain vascular imaging (31% of 63). Definable arteriopathies were small vessel disease secondary to CNS infection (50%), transient cerebral arteriopathy (25%), arterial dissection (15%), and moyamoya disease (10%).

In the multivariate Cox analysis, age, AS, cortical involvement, and multifocal infarction were still independent factors associated with higher risk to develop epilepsy (Table 2). In contrast, neither arteriopathies nor involvement of the MCA territory is associated with an increased risk of PSE. Also, multivariate Cox regression analyses demonstrated that the adjusted risk of epilepsy decreased 8% for each 1-year increase in age.

Table 1
Baseline clinical and radiological characteristics of children with a first AIS.

	Frequency			Frequency	
Clinical characteristics	Number	Percentage	Stroke characteristics	Number	Percentage
Demographics			**Infarct location**		
Age at onset <1 year	39	39.9	Cerebral cortex	60	61.2
Female	38	38.8	Internal capsule	28	28.6
Male	60	61.2	Corona radiata	67	68.4
Clinical manifestations			Corpus callosum	30	30.6
Acute symptomatic seizures	52	53.1	Basal ganglia	38.8	38
GCS < 12 at diagnosis	72	73.5	Thalamus	25	25.5
Focal deficits			Cerebellum	6	6.1
Motor deficit	44	44.9	Brainstem	8	8.2
Language deficit	17	17.3	Frontal	74	75.5
Visual deficit	9	9.2	Parietal	46	46.9
Cranial nerve deficit	9	9.2	Temporal	22	22.4
Headache	16	16.3	Occipital	36	36.7
Underlying conditions			**Arterial territory involved**		
Cardiopathy	37	37.8	Anterior cerebral artery	42	42.9
Congenital	27	27.6	Middle cerebral artery	65	66.3
Acquired	10	10.2	Posterior cerebral artery	37	37.8
CNS arteriopathy	20	20.4	Vertebrobasilar	11	11.2
Infections	38	38.8	**Infarct number**		
Mild systemic infection	28	28.6	Unifocal	36	36.8
CNS infections	10	10.2	Multifocal	62	63.3
Shock	23	23.5	**Laterality**		
Chronic conditions	32	32.7	Bilateral	50	51
Neoplasms	7	7.1	Left hemisphere	28	28.6
Anemia	15	15.3	Right hemisphere	20	20.4
Prothrombotic states	20	20.4	**Hemorrhagic transformation**	11	11.2

Abbreviations: GCS: Glasgow coma scale; CNS: central nervous system; BG: basal ganglia.