

## Factors associated with ischemic stroke in children and adolescents with tetralogy of Fallot

*Fatores associados ao acidente vascular cerebral isquêmico em crianças e adolescentes com tetralogia de Fallot*

*Factores asociados con accidente vascular cerebral isquémico en niños y adolescentes con tetralogía Fallot*

### ABSTRACT

**Objective:** to verify the factors associated with ischemic stroke in children and adolescents with tetralogy of Fallot. **Method:** a cross-sectional study, carried out with analysis of electronic medical records of children and adolescents with tetralogy of Fallot followed up in an outpatient clinic specialized in pediatric cardiology in northeastern Brazil. The data was processed in SPSS 21.0. Chi-square and/or Fisher's exact test were used for association measures ( $p \leq 0.05$ ). **Results:** of the 104 electronic medical records analyzed, ischemic stroke in the bivariate analysis was associated with hypothyroidism, thrombophilia, polycythemia, endocarditis, cardiac arrest, acute renal failure and heart failure. In the final multivariate analysis model, thrombophilia ( $p=0.011$ ), polycythemia ( $p < 0.001$ ) and cardiac arrest ( $p=0.005$ ) were predictors of ischemic stroke. **Conclusion:** thrombophilia, polycythemia, and cardiac arrest were associated with ischemic stroke in children and adolescents with tetralogy of Fallot.

**Descriptors:** Stroke; Tetralogy of Fallot; Child; Adolescent; Congenital Heart Disease.

### RESUMO

**Objetivo:** verificar os fatores associados ao acidente vascular cerebral isquêmico em crianças e adolescentes com tetralogia de Fallot. **Método:** estudo transversal, realizado com análise dos prontuários eletrônicos de crianças e adolescentes com tetralogia de Fallot acompanhados em um ambulatório especializado em cardiologia pediátrica no nordeste brasileiro. Os dados foram processados no SPSS 21.0. Aplicou-se Teste Qui-quadrado e/ou Exato de Fisher para medidas de associação ( $p \leq 0,05$ ). **Resultados:** dos 104 prontuários eletrônicos analisados, o acidente vascular cerebral isquêmico na análise bivariada foi associado com hipotireoidismo, trombofilia, policitemia, endocardite, parada cardiorrespiratória, insuficiência renal aguda e insuficiência cardíaca. No modelo final da análise multivariada, foram preditores de acidente vascular cerebral isquêmico a trombofilia ( $p=0,011$ ), policitemia ( $p < 0,001$ ) e parada cardiorrespiratória ( $p=0,005$ ). **Conclusão:** trombofilia, policitemia e a parada cardiorrespiratória foram associados ao acidente vascular cerebral isquêmico em crianças e adolescentes com tetralogia de Fallot.


**Descritores:** Acidente Vascular Cerebral; Tetralogia de Fallot; Criança; Adolescente; Cardiopatias Congênitas.

### RESUMEN


**Objetivo:** verificar los factores asociados al ictus isquémico en niños y adolescentes con tetralogía de Fallot. **Método:** estudio transversal, realizado con análisis de registros médicos electrónicos de niños y adolescentes con tetralogía de Fallot seguidos en una consulta externa especializada en cardiología pediátrica en el noreste de Brasil. Los datos se procesaron en SPSS 21.0. Para las medidas de asociación se utilizó la prueba de Chi-cuadrado y / o Exacta de Fisher ( $p \leq 0.05$ ). **Resultados:** de las 104 historias clínicas electrónicas analizadas, el ictus isquémico en el análisis bivariado se asoció con hipotiroidismo, trombofilia, policitemia y las complicaciones fueron endocarditis, parada cardiorrespiratoria, insuficiencia renal aguda e insuficiencia cardíaca. En el modelo final del análisis multivariado, los predictores de ictus isquémico fueron trombofilia ( $p = 0,011$ ), policitemia ( $p < 0,001$ ) y paro cardíaco ( $p = 0,005$ ). **Conclusión:** la trombofilia, la policitemia y el paro cardiorrespiratorio se asociaron al ictus isquémico en niños y adolescentes con tetralogía de Fallot.

**Descritores:** Accidente Cerebrovascular; Tetralogía de Fallot; Niño; Adolescente; Cardiopatías Congénitas.


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## INTRODUCTION

Congenital heart disease remains a serious public health problem<sup>(1)</sup>, due to the high rates of morbidity and mortality. Among them, there is the tetralogy of Fallot (T4F), a critical congenital heart disease (CCH) consisting of the associated presence of interventricular communication, aortic dextroposition, right ventricular obstruction, and right ventricular hypertrophy<sup>(2)</sup> that together bring severe hemodynamic repercussions, unfavorably influencing the clinical outcome of affected individuals, when surgical treatment is not performed in a timely manner. Among these outcomes is ischemic stroke, which has a high morbidity and mortality rate in children and adolescents<sup>(3)</sup>.

Critical Congenital Heart Disease has a worldwide incidence of 5 to 8 cases per thousand live births, with T4F accounting for 7 to 10%<sup>(4)</sup>. Therefore, early diagnosis and treatment is important to improve the survival of children and adolescents affected and avoid complications such as stroke<sup>(3)</sup>. However, the diagnosis of ischemic stroke is late in most affected children, justified by the lack of familiarity, the non-specificity and wide range of symptoms, the non-availability of neuroimaging modalities and the lack of scientific evidence in acute treatments<sup>(5)</sup>.

In view of the above, there is the importance of the theme for public health, since ischemic stroke has serious repercussions on the quality of life and survival of children and adolescents, with increased costs for the health sector, due to frequent hospitalizations and rehabilitation in case of sequelae and/or dysfunctions, in addition to school absenteeism and early loss of life<sup>(6)</sup>.

To reverse this situation, it is essential that health professionals, especially nurses, recognize the main clinical factors and complications associated with ischemic stroke in T4F, in order to enable the adoption of specific preventive measures, such as early warning and treatment of initial symptoms, as well as monitoring and rehabilitation of cases. The nurse is an important professional in the care provided with the inter-professional team, and often the link between patient/family and team.

Despite the importance of the theme, it was noticed a scarcity of scientific production, especially related to ischemic stroke in children and adolescents with tetralogy of Fallot. Through the bibliographical survey in the databases of the Virtual Health Library (VHL) and PubMed using the descriptors and MeSH: Tetralogy of Fallot, stroke,

ischemic stroke, stroke pediatric, child and adolescent, it was observed a gap related to the theme, being found two articles and all findings were international<sup>(7-8)</sup>.

The investigated hypothesis is that there is a relationship between T4F and ischemic stroke in children and adolescents. Given the above, the research question is: what are the factors associated with ischemic stroke in children and adolescents with tetralogy of Fallot?

Thus, the aim of this study was to verify the factors associated with ischemic stroke in children and adolescents with tetralogy of Fallot.

## METHODS

This is an epidemiological, cross-sectional, analytical study, guided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative; conducted in a referral outpatient clinic in cardiology and pediatric cardiovascular surgery of a private hospital affiliated with the Brazilian Unified Health System (UHS) in Northeastern Brazil.

The population of this study consisted of a non-probabilistic sample represented by electronic medical records of children and adolescents aged 0-19 years with a medical diagnosis of FT4, followed up at the locus of the study, from various municipalities of the state of Bahia (417 municipalities) and other states in the northeast region and referred through the UHS to the Specialized Outpatient Clinic.

Data collection occurred between April 2017 to December 2019, was performed in the electronic medical record, on the same day of follow-up of children and adolescents in the outpatient clinic. The consultation of electronic medical records was guided by a form of our own elaboration. Inclusion criteria were all available medical records of children and adolescents with a medical diagnosis of T4F. Exclusion criteria were other congenital heart diseases (except T4F) and acquired heart diseases.

Ischemic stroke was the dependent variable, identified in the medical chart through the International Classification of Diseases - ICD 163. The independent variables were: age group, gender, age at ischemic stroke, morbidities (Hypothyroidism, Down's syndrome, Thrombophilia and Polycythemia), types of congenital alterations in the heart (besides T4F alterations) and complications (Endocarditis, Cardiorespiratory arrest, Acute Renal Failure and Heart Failure).

The data collected was processed in the Statistical Program for Social Sciences (SPSS) version 21.0. Kolmogorov-Smirnov was used to test the normality of the variables. Frequencies and percentages were calculated for categorical variables. Bivariate analysis was performed using Pearson's Chi-square ( $\chi^2$ ) and/or Fisher's exact test to assess possible statistical significance between ischemic stroke and the independent variables.

All variables worked in the bivariate analysis were included in the multivariate model. Multivariate associations were tested using logistic regression models, with Stepwise criteria for variable selection, according to the statistical significance level of  $p \leq 0.05$ .

The project was approved by the local Research Ethics Committee, under opinion number

2.315.187 and CAAE: 64329817.2.0000.5520, meeting the guidelines of Resolution 466/12 of the National Health Council. Due to the retrospective data collection in database, and unfeasibility of obtaining the free and informed consent term (FICT), the waiver of the FICT was authorized by the REC, and the respect, anonymity and confidentiality of the participants were ensured.

## RESULTS

Data was collected from 104 medical records of children and adolescents with T4F from the pediatric cardiology outpatient clinic, ischemic stroke was evidenced in 07 (6.7%). The association data of clinical characterization and complications of the population are described in Table 1.

Table 1 - Association of clinical characteristics and complications of children and adolescents with tetralogy of Fallot according to ischemic stroke (2017-2019). Salvador, BA, Brazil, 2019

Characteristics	Total N=104 (n%)	Ischemic Stroke n (%)		p-value
		Yes (n=7)	No (n=97)	
Age group years -n (%)				
< 1 year	4 (3.8)	-	4 (4.1)	
1 - 4	20 (19.3)	1 (14.3)	19 (19.6)	0.802
5 - 9	29 (27.9)	2 (28.6)	27 (27.8)	
10-19	51 (49.0)	4 (57.1)	47 (48.5)	
Sex- n (%)				
Male	62 (59.6)	3 (42.9)	59 (60.8)	0.349
Female	42 (40.4)	4 (57.1)	38 (39.2)	
Morbidities-n (%)*				
Hypothyroidism	6 (5.8)	2 (28.6)	4 (4.1)	0.007
Down syndrome	3 (2.9)	-	3 (3.1)	0.637
Thrombophilia	1 (1.0)	1 (14.3)	-	<0.001
Polycythemia	1 (1.0)	1 (14.3)	-	<0.001
Congenital heart diseases -n (%)†				
Interatrial Communication (IAC)	10 (9.6)	-	10 (10.3)	0.372
Patent Foramen Oval (PFO)	10 (9.6)	1 (14.3)	9 (9.3)	0.664
Pulmonary Atresia	8 (7.7)	1 (14.3)	7 (7.2)	0.498
Persistent Ductus Arteriosus (PDA)	5 (4.8)	-	5 (5.2)	0.538
Complications-n (%)‡				
Endocarditis	3 (2.9)	2 (28.6)	1 (1.0)	<0.001
Cardiopulmonary arrest	2 (1.9)	2 (28.6)	-	<0.001
Acute Renal Failure	1 (1.0)	1 (14.3)	-	<0.001
Heart Failure	2 (1.9)	1 (14.3)	1 (1.0)	0.014

Note: \*Morbidities- n (%): Only those who presented the cited morbidities.

†Congenital heart diseases- n (%): Only those who presented the cited heart diseases.

‡Complications- n (%): Only those who presented the cited complications.

Source: Research data

In the multivariate analysis, the variables that were associated with ischemic stroke were included in the bivariate model, and it was found in the final model that the presence of thrombophilia,

polycythemia and, as a complication, cardiac arrest (CA) were independent predictors for ischemic stroke (Table 2).

Table 2 - Multivariate analysis of morbidities and complications associated with ischemic stroke in children and adolescents with tetralogy of Fallot (2017-2019). Salvador, BA, Brazil, 2019

Variables	Initial model	Final model
	p-value	p-value
Morbidades		
Thrombophilia	0.008	0.011
Polycythemia	0.001	<0.001
Complications		
Cardiopulmonary arrest	0.239	0.005
Endocarditis	0.056	
Acute Renal Failure	0.999	

Source: Research data

## DISCUSSION

It is possible to observe from the results brought in our study that there was a prevalence of 6.7% of ischemic stroke in the studied population, although our prevalence was lower when compared to another study<sup>(9)</sup>, we attribute this to the follow-up in a specialized outpatient clinic, with a multi-professional team, which favors a continuous monitoring of the heart disease and consequent reduction of its complications. But these complications are still possible even if they occur in adolescence, as were the cases that we found more adolescents (10-19 years old) affected by ischemic stroke.

Clinical factors such as morbidities, thrombophilia, and polycythemia were predictors of ischemic stroke in children and adolescents with T4F. These factors have been signaled in other studies of patients with cyanogenic congenital heart disease, present compensatory adaptive mechanism that aims to increase the oxygen-carrying capacity, by increasing the erythrocyte mass, but that causes the hyperviscosity of the blood and that results in counterpart in decreased blood flow and tissue hypoperfusion, enabling the emergence of cardiovascular complications and thromboembolic events<sup>(10)</sup>. This adaptive process can lead to the formation and release of a thrombus, which can cause an obstruction of a cerebral vessel, leading to an ischemic stroke.

Endocarditis was one of the complications found in our study, although there was no statistical significance in multivariate analysis, this complication was frequent, which can be attributed, in addition to heart disease, to the vulnerability of our sample. In a retrospective observational study conducted in the United Kingdom and in the Republic of Ireland for a period of eight years, they found that of 800 hospitalizations for infective endocarditis, 736 were patients with congenital heart diseases, the most common being tetralogy of Fallot in 150

(22.8%)<sup>(11)</sup>, highlighting the complexity of heart disease, frequent surgical interventions and the use of prosthetic cardiac material, which requires immediate intervention by health professionals, especially nurses, in patients who have prosthetic cardiac material and present prolonged and unexplained febrile conditions, as pointed out by international authors<sup>(12)</sup>.

Another complication associated with ischemic stroke was CRA, which corroborates a French study that evidences that sudden cardiac death may occur late in T4F and may be linked to ventricular arrhythmias<sup>(13)</sup>. In a multicenter cohort, survival after surgical repair of tetralogy of Fallot was investigated and the risk factors associated with mortality were ventricular arrhythmias and congestive heart failure<sup>(14)</sup>, despite the cases of CRA in our study, these did not evolve to death in our population.

Regarding ARF, evidence in the literature<sup>(15-16)</sup>, The researches point out that the elevation of preoperative serum creatinine, age less than 1 year, lower body weight at surgery, nephrotoxic drugs, complexity of surgical correction, longer cardiopulmonary bypass (CPB) time, and low cardiac output syndrome after surgical correction are risk factors for acute kidney injury in children and adolescents with cyanogenic congenital heart diseases, being recommended immediate postoperative care in cardiac surgery in order to avoid possible complications.

Heart failure (HF) was shown to be associated with the dependent variable in this study. In a cohort conducted by Bond et al.<sup>(17)</sup>, in the United Kingdom showed that HF in children with T4F may occur even before surgical repair, due to long persistent D ventricular outflow obstruction, or even after surgical repair of T4F, a condition that can be potentiated due to right ventricular (RV) overload caused by severe pulmonary valve regurgitation and residual flow obstruction. Corroborating the findings of this

study, in a cohort conducted in a pediatric hospital in Switzerland, points out that in 24% of patients with T4F after cardiac approach present progressive RV dilatation, considered a major cause of morbidity and mortality in this population, affecting mainly adolescents and young adults<sup>(18-19)</sup>.

Therefore, to avoid outcomes such as ischemic stroke in children and adolescents with T4F, it is necessary to use strategies such as early diagnosis and treatment (surgical approach) and periodic follow-up in the specialized outpatient clinic<sup>(20)</sup>, in which it is fundamental for health professionals, among them nurses, to have knowledge about the clinical factors and complications associated with ischemic stroke in this population and intervene early in order to avoid unfavorable prognoses and possible sequelae.

Therefore, the results found will contribute to the identification and understanding of factors associated with ischemic stroke in children and adolescents with T4F. Within this context, nurses can act in the identification of potential risks of ischemic stroke and act in the recognition of the clinical picture and problems caused by this event, both at the hospital level and in primary health care, during follow-up consultations and development. At the outpatient level, the nurse can perform telemonitoring with the purpose of health education, acting in prevention and orienting the parents/caregivers about ischemic stroke and the warning signs, and if they are present, to guide in the immediate search for health services. Thus, by identifying these factors early, nurses, at different levels of complexity, should refer these children and adolescents to specialized health services, in order to reduce morbidity and mortality from ischemic stroke and its possible sequelae/complications.

Future randomized studies that can evaluate the effectiveness of close monitoring of these children and adolescents by health professionals are suggested, so that they do not arrive late in specialized services, because cyanogenic congenital heart diseases are causes of high rates of morbidity and mortality for the neurological disorder studied. In addition, it is recommended that the investigation be extended to other outpatient clinics specialized in cardiology and pediatric cardiovascular surgery.

A limitation of the study is the fact that it was designed in only one specialized center. However, 100% of the population of the center, which is a

reference in the Northeast of Brazil, was studied. In addition, previous studies do not present the object investigated here, which gives the present study an unprecedented and relevant contribution to the state of the art of the theme.

## CONCLUSION

The study shows that clinical factors such as thrombophilia and polycythemia and cardiac arrest as a complication were predictors of ischemic stroke in children and adolescents with T4F.

Recognizing the clinical factors and complications associated with ischemic stroke in children and adolescents with T4F may improve survival, physical and social well-being, and the bond of trust between nurses and family members of these children and adolescents. Therefore, it is essential that they have a strict monitoring and control in the prevention of this event in specialized services and primary health care, including when they reach adulthood.

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