



## Original Article

# Pediatric Infective Endocarditis and Stroke: A 13-Year Single-Center Review

Gui-fang Cao, MD\*, Qi Bi, MD

Department of Neurology, Beijing Anzhen Hospital Affiliated to Capital Medical University, Beijing, China

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## ABSTRACT

**OBJECTIVE:** We explored the relationship between pediatric infective endocarditis and stroke.

**PATIENTS AND METHODS:** All children encountered with infective endocarditis from January 2002 to December 2015 were included as our sample, and their medical records were comprehensively reviewed.

**RESULTS:** Sixty children with infective endocarditis were identified, including 30 boys and 30 girls aged eight months to 18 years (mean  $\pm$  SD: 10.3  $\pm$  5.6), and 43 (71.6%) of these individuals had congenital heart disease. Left-sided endocarditis occurred in 25 patients (41.7%), and vegetations were found in 58 individuals (96.6%). The most often encountered microorganisms were *Streptococcus viridans* and *Staphylococcus aureus*, which were identified in five and four patients, respectively. Postendocarditis stroke occurred in nine patients, including five with cerebral infarction, two with intracerebral hemorrhage, and one with subarachnoid hemorrhage. The remaining child experienced cerebral infarction, intracerebral hemorrhage and subarachnoid hemorrhage simultaneously. The incidence of stroke in children with left-sided endocarditis was significantly higher than that of which in those who had right-sided endocarditis (32% versus 2.8%,  $P < 0.01$ ). The most common manifestation of stroke was hemiparesis (55.5%). Two girls died of stroke, and the mortality rate in the patients who had stroke was significantly higher than that in those without stroke (22.2% versus 3.9%,  $P < 0.05$ ).

**CONCLUSIONS:** Our data indicate that stroke is common among children with infective endocarditis, especially in those with left-sided endocarditis, and major stroke may increase their risk of death. Congenital heart disease is the main underlying disease in children with infective endocarditis in China.

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## Introduction

Although stroke is uncommon in children, it is an important cause of acquired brain injury for this specific population. Stroke is associated with a high mortality rate, leaving neurological sequelae in more than 50% of cases.<sup>1</sup> It has

been shown that infective endocarditis is an important cause of stroke in young adults, resulting in neurological complications in 20% to 40% of the patients.<sup>2,3</sup> However, little attention has been paid to the relationship between infective endocarditis and stroke among children.

Infective endocarditis rarely occurs in children. In a recent multicenter report,<sup>4</sup> its annual incidence in the United States was between 0.05 and 0.12 per 1000 pediatric admissions from 2003 to 2010, without any significant trend. Because in most retrospective studies children and adults have been analyzed as a single cohort, it has been difficult to distinguish clinical variables specific to

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\* Communications should be addressed to: Gui-fang Cao; Department of Neurology; Beijing Anzhen Hospital Affiliated to Capital Medical University; Anzhen Road 2; Beijing 100029; China.

E-mail address: [caoguifang2013@sina.cn](mailto:caoguifang2013@sina.cn)

children.<sup>5,6</sup> We analyzed the clinical data of children less than 18 years of age who were hospitalized with infective endocarditis in recent years in order to summarize their clinical characteristics.

## Patients and Methods

This analysis was conducted at Beijing Anzhen Hospital affiliated to Capital Medical University, the National Clinical Research Center of Cardiovascular Diseases in China. Medical records were obtained with International Classification of Diseases codes identifying all patients aged less than 18 years who had been diagnosed with infective endocarditis and admitted between January 2002 and December 2015. The definition of infective endocarditis was based on modified Duke criteria, and stroke was defined as positive findings of infarction or bleeding by computed tomography (CT) or magnetic resonance imaging (MRI). Both ischemic and hemorrhagic strokes were included in this study. Comprehensive demographic and clinical details were obtained from the hospital records.

Statistical methods: A descriptive study was used. Frequency data were assessed with chi-square. A two-tailed *P*-value of less than 0.05 was considered statistically significant.

## Results

### Demographic characteristic of patients

Sixty children (30 boys and 30 girls), aged eight months to 18 years (average:  $10.3 \pm 5.6$  years), with infective endocarditis were identified.

### Other complications during the course of disease

Forty-six children (76.6%) had other coexisting complications (see Table 1). Forty-three patients 43 (71.6%) were diagnosed with congenital heart disease, including 26 (43.3%) with ventricular septal defect (VSD); four (6.7%) with atrial septal defect; four (6.7%) with patent ductus arteriosus; three (5.0%) with patent foramen ovale; three (5.0%) with tetralogy of Fallot; six (10.0%) with bicuspid aortic valves; and three (5.0%) with coarctation of the aorta. Ten children had undergone previous cardiac procedures for congenital heart disease. Mitral valve prolapse (3.3%) and Behcet disease (1.7%) were documented in a few patients.

### Clinical manifestation

Fever was present in 39 patients (see Table 2). Mild or modest anemia was present in 40 patients (66.7%), and

**TABLE 1.** The Underlying Disease of 60 Children with Infective Endocarditis

Underlying Disease	Patients (Percent)
Congenital heart disease	43 (71.6%)
Ventricular septal defect	26 (43.3%)
Atrial septal defect	4 (6.7%)
Patent ductus arteriosus	4 (6.7%)
Patent foramen ovale	3 (5.0%)
Tetralogy of fallot	3 (5.0%)
Bicuspid aortic valves	6 (10.0%)
Coarctation of the aorta	3 (5.0%)
Mitral valve prolapse	2 (3.3%)
Behcet disease	1 (1.7%)
TOTAL	46 (76.6%)

**TABLE 2.** The Clinical Features of 60 Children with Infective Endocarditis

Clinical Features	Patients (Percent)
Fever	39 (65.0%)
Anemia	40 (66.7%)
Congestive heart failure	9 (15.0%)
Embolism of extremity	3 (5.0%)
Pulmonary embolism	1 (1.7%)
Stroke	9 (15.0%)
Death	4 (6.7%)

congestive heart failure was found in nine children (15.0%). A total of four children had venous thromboembolism (three with deep vein thrombosis and one with pulmonary embolism). A total of nine (15%) patients experienced stroke.

Four patients died in hospital, among whom two died of septic shock and associated multiorgan failure, one died of intracerebral hemorrhage (ICH), and the remaining individual died of combined syndromes of ICH, subarachnoid hemorrhage (SAH), and cerebral infarction.

### Vegetation and other echocardiographic findings

Left-sided endocarditis occurred in 25 patients (41.7%), and 35 patients (58.3%) had right-sided endocarditis. Vegetation was found in 58 patients (96.6%), of which nine (15.0%) were located at aortic valves, 14 (23.3%) at mitral valves, 14 (23.3%) at tricuspid valves, nine (15.0%) at pulmonary valves, five (8.3%) at right ventricle, and seven (11.7%) at other locations (see Table 3).

Twenty-six patients (43.3%) experienced regurgitation. Rupture of chordae tendinea, valve perforation, and abscess below the valve were found in four (6.7%), six (10.0%), and one patient (1.7%), respectively.

### Blood cultures

Blood cultures were obtained in 48 of 60 children with endocarditis. The positive rate of blood culture was 37.5% (see Table 4), as microorganisms were found in 18 of the 48 blood cultures, and the first and second commonest ones are *Streptococcus viridians* and *Staphylococcus*

**TABLE 3.** The Location of Vegetation and Other Echocardiographic Findings of 60 Children with Infective Endocarditis

Items	Patients (Percent)
Location of infective endocarditis	
Left	25 (41.7%)
Right	35 (58.3%)
Vegetation	58 (96.4%)
Aortic valves	9 (15.0%)
Mitral valves	14 (23.3%)
Tricuspid valves	14 (23.3%)
Pulmonary valves	9 (15.0%)
Right ventricle	5 (8.3%)
Other location	7 (11.7%)
Other echocardiographic findings	
Regurgitation	26 (43.3%)
Rupture of chordae tendinea	4 (6.7%)
Valve perforation	6 (10.0%)
Abscess below the valve	1 (1.7%)

**TABLE 4.** The Blood Cultures of Children with Infective Endocarditis

Items	Patients (Percent)
Blood cultures	48 (80.0%)
Microorganism identified	18 (37.5%)
<i>Streptococcus viridans</i>	5 (10.4%)
<i>Staphylococcus aureus</i>	4 (8.3%)
<i>Streptococcus mitis</i>	2 (4.2%)
<i>Staphylococcus sciuri</i>	1 (2.1%)
<i>Staphylococcus epidermidis</i>	2 (4.2%)
<i>Staphylococcus haemolyticus</i>	1 (2.1%)
<i>Stenotrophomonas maltophilia</i>	1 (2.1%)
<i>Escherichia coli</i>	1 (2.1%)
<i>Candida glabrata</i>	1 (2.1%)
No microorganism identified	30 (62.5%)

*aureus*, which are identified in five and four blood samples, respectively.

#### Specific characteristic of the stroke cases

Six girls and three boys, aged from one to 16 years, experienced a stroke (see Table 5), among whom five (three males, two females) were diagnosed with cerebral infarction, two (one male, one female) with ICH, one (female) with SAH. The remaining female patient experienced combined cerebral infarction, ICH, and SAH.

VSD was present in four stroke patients, three of whom had undergone surgical repair. The remaining five patients had no known underlying disease. Eight patients had left-sided endocarditis, with vegetation at the mitral valve and the aortic valve in five and three cases, respectively. Only one stroke patient's infective endocarditis occurred on the right side, and its associated vegetation was located at the tricuspid valve. The incidence of stroke in children with the left-sided endocarditis was significantly higher than that of which in those whose endocarditis occurred at the right side (32% versus 2.8%,  $P < 0.01$ )

Hemiparesis was the most common neurological sign of stroke, occurring in five individuals (55.5%). Other

symptoms, such as seizures, dizziness, headache, and aphasia were also exhibited by some patients. One girl died of ICH, and another girl died from cerebral infarction plus ICH and SAH. The mortality rate of the patients with stroke was significantly higher than that of those without stroke (22.2% versus 3.9%,  $P < 0.05$ ).

Eight patients received prolonged intravenous antibiotic therapy (two to four weeks) before admission. Blood cultures were available in six individuals, among which pathogens, *Escherichia coli* and *Candida glabrata*, were separately identified in two of them.

#### Discussion

We identified 60 pediatric patients with infective endocarditis during the past 13 years, and nine of these individuals (15.0%) experienced a stroke, including five (8.3%) with cerebral infarction, three with brain hemorrhage (5%, two ICHs and one SAH), and one patient who exhibited combined cerebral infarction, ICH, and SAH.

Currently, there is insufficient literature to pinpoint the stroke incidence among children with infective endocarditis. Asakai et al.<sup>7</sup> retrospectively reviewed 76 children in whom cardiac disease and stroke concurrently occurred. Among those cases, three (4%) were diagnosed with infective endocarditis. In another retrospective analysis conducted by Venkatesan et al.,<sup>8</sup> the stroke incidence in children with infective endocarditis was approximately 6%. Compared with their result, our stroke rate (15.0%) is higher.

Stroke mainly occurred in patients affected by left-sided endocarditis in our sample, which amounts to a total of 25 in counts. The incidence of stroke in patients with the left-sided endocarditis was significantly higher than that of which in those affected by endocarditis on the right side (32% versus 2.8%). This statistic implies that stroke was more common in children with left-sided endocarditis. Okazaki et al.<sup>9</sup> evaluated the brain lesions

**TABLE 5.** Clinical Features of Children with Stroke

Patients	Sex	Age(yr)	Organism	Cardiac History	Location of Vegetation	Stroke Type	Vessel Involved	Neurological Findings	Death
1	Female	10	Culture negative	VSD	MV	CI	Left MCA	Right hemiparesis; seizure	No
2	Female	11	Culture negative	VSD, repaired	AV	SAH	N/A	Headache	No
3	Female	1	Culture negative	VSD, repaired	TV	ICH	Right MCA	Left hemiparesis	Yes
4	Female	16	N/A	None	MV	CI	VBA	Dizziness	No
5	Female	16	N/A	None	AV	CI	Left ICA	Right hemiparesis	No
6	Male	16	Culture negative	None	AV	ICH	Left MCA	Headache; seizure	No
7	Male	15	N/A	None	MV	CI	Left ICA	Right hemiparesis, Broca aphasia	No
8	Female	1	<i>Candida glabrata</i>	VSD, repaired	MV	ICH /CI/SAH	Both ICA	Coma, seizure	Yes
9	Male	16	<i>Escherichia coli</i>	None	MV	CI	Both ICA	Headache, right hemiplegia	No

#### Abbreviations:

AV = Aortic valve

CI = Cerebral infarction

ICA = Internal carotid artery

ICH = intracerebral hemorrhage

MCA = Middle cerebral artery

MV = Mitral valve

N/A = Not available

SAH = Subarachnoid hemorrhage

TV = Tricuspid valve

VBA = Vertebral basilar artery

VSD = Ventricular septal defect

in 85 adult patients with left-sided infective endocarditis by preoperative brain MRI, among whom 47 (55%) were found with acute ischemic cerebral lesions, and only 19 cases had symptoms of ischemic stroke. In our series, only patients with neurological symptom were screened by cranial CT or MRI. Therefore, the exact occurrence of stroke may be underestimated as asymptomatic stroke patients who did not go through neuroimaging may be neglected from diagnosis.

The stroke lesions in our sample were not only found in the middle cerebral artery and the internal carotid artery but also in the vertebral basilar system. Okazaki et al.<sup>9</sup> reported 47 patients with infective endocarditis accompanied by acute ischemic cerebral lesions, of whom 28 had cerebral infarction in the tissues supplied by the vertebro-basilar system. Our findings and those of Okazaki et al. demonstrate that posterior circulation cerebral infarction is not uncommon in patients with infective endocarditis. Cardioembolic strokes may occur any of the cerebral artery territories.

Hemiparesis and seizures were the most common neurological complications in our sample, and this result is in line with the reports by Venkatesan et al.<sup>8,10</sup> However, in our study, some patients underwent brain imaging in response to symptoms such as headache and dizziness.

Our data showed that hemorrhagic stroke was not rare in children with infective endocarditis, as especially exemplified by the girl who simultaneously experienced cerebral infarction, cerebral hemorrhage, and SAH. Hemorrhagic stroke may complicate the state of infection by one of the following mechanisms: blood vessel wall damage by infectious emboli, rupture of intracranial infective aneurysms, hemorrhagic transformation of infarction lesions, and anticoagulant effects. Because none of our patients had an apparent cerebral infarction before hemorrhagic stroke, the possibility of hemorrhagic transformation following an infarction lesions was diminished. Three children with hemorrhagic stroke did not undergo anticoagulant treatment, suggesting that anticoagulants are not the most significant risk factor for hemorrhage.

Intracranial infective aneurysms are relatively rare, accounting for less than 10% of the neurological complications caused by infective endocarditis.<sup>11</sup> Flor-de-Lima et al.<sup>12</sup> reported one adolescent with hemorrhagic stroke due to rupture of an infective aneurysm. Strokes were usually caused by septic embolization in the vasa vasorum or in the intraluminal space of the vessel itself. CT-scan and MR angiography are of equal value for the detection of mycotic aneurysms. SAHs presented in two girls from our sample were thought to be caused by intracranial mycotic aneurysms. Unfortunately, these patients did not undergo either MR angiography or CT angiography.

Vegetations were identified by color Doppler echocardiography in all nine children who experienced stroke, primarily affecting the mitral valves (five patients) and aortic valves (three patients). Walker et al.<sup>13</sup> reviewed 18 patients who experienced acute a stroke with positive diagnoses of infective endocarditis in most of them. Vegetation (11 in the mitral valve, three in the aortic valve,

one in both mitral and aortic valve, one in the tricuspid valve) were found by transthoracic echocardiogram and/or transesophageal echocardiogram in 16 individuals. Abnormal tissue formation at the mitral valve may increase the risk of stroke for patients with infective endocarditis. Our results suggest that patients with an endocarditis-induced vegetation at the mitral valves and/or aortic valves (left-sided endocarditis) have a higher probability of having stroke than patients with vegetation elsewhere ( $P < 0.05$ ).

In developing countries, rheumatic heart disease remains the most common disease underlying infective endocarditis,<sup>14</sup> while in developed countries congenital heart disease is more prevalent as the comorbidity of infective endocarditis. Johnson et al.<sup>10</sup> retrospectively reviewed 47 patients less than 20 years of age who were diagnosed with infective endocarditis at Mayo Clinic, and 36 (77%) of them had congenital heart disease. However, a majority of our patients with infective endocarditis (71.6%) had congenital heart disease, and VSD accounted for more than 40% of the cases of congenital heart disease. This distribution is similar to infected populations in the developed countries. This convergence with the western world may be owing to the increased screening for congenital heart diseases and better prevention of rheumatic fever in our country.

Positive blood cultures were present in only 37.5% of the patients with infective endocarditis. Studies from the Indian subcontinent had comparable figures, varying from 21% to 47%,<sup>15</sup> while reports from the Western literature showed a positivity rate of over 90%.<sup>12,16</sup> Prior antibiotic treatment was the major cause of negative blood cultures, occurring in more than 50% of the patients. *Streptococcus viridans* and *S. aureus* were the most common pathogenic bacteria.

*S. aureus* was reported to be associated with an increased risk of embolism and stroke.<sup>17</sup> In our study, because of prior exposure to antibiotics and insufficient blood cultures, pathogens (*C. grabrata* and *E. coli*) were identified only in two stroke patients. Due to this lack of data, *S. aureus* infection's impact on the risk of stroke could not be further analyzed.

Stroke may increase the mortality of patients with infective endocarditis. According to Lee et al.'s<sup>18</sup> analysis of 144 patients with left-sided endocarditis, the major stroke group (with an initial modified Rankin scale  $\geq 3$ ) had a higher mortality than the no-stroke group ( $P=0.013$ ; hazard ratio 2.865; confidence interval 1.254 to 6.548). In our study, two girls, both one-year-old, died of stroke, and both of them suffered from ICH. The mortality rate of the patients with stroke was significantly higher than that of those without (22.2% versus 3.9%,  $P < 0.05$ ). Thus, major stroke may increase the risk of death for children with infective endocarditis.

Our study has inherent limitations. First, our rather small sample size limited the scope of statistical analyses. Second, its retrospective nature compromised the data integrity to a certain degree, as necessary statistics were derived from the medical records. Finally, only patients with neurological symptoms underwent neuroimaging in our sample, resulting in missed or misdiagnoses of some

atypical or asymptomatic stroke patients. Therefore, the actual incidence of stroke may be underestimated.

## Conclusions

Stroke is a common complication among children with infective endocarditis, especially for those with endocarditis affecting the left side. Major stroke may have a major impact on their life expectancy. Congenital heart disease is the main underlying disease in children with infective endocarditis in China.

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