


Clinical Characteristics and Thrombolytic Outcomes of Infective Endocarditis-Associated Stroke

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Abstract

Objective: Our aim was to describe the clinical features of infective endocarditis (IE) in the acute stroke setting and outcomes following thrombolytic therapy. **Methods:** This is a single-center, retrospective, descriptive case series of IE-related stroke (IES). Infective endocarditis diagnosis was based on the modified Duke criteria. **Results:** From 2001 to 2007, 18 patients with acute stroke had definite or possible IE. Presenting stroke subtypes were: 11 ischemic stroke; 2 intracerebral hemorrhage; and 5 with a combination of ischemia and subarachnoid hemorrhage. On presentation, 6 had objective fever and 5 had subjective fever, 8 had heart murmur, and 3 had classic IE stigmata. The most common laboratory abnormalities were leukocytosis ($n = 11$) and anemia ($n = 10$). Sixteen patients had valvular vegetations on echocardiogram; 6 of 8 patients had vegetations visualized on transesophageal echocardiogram that were not detected by transthoracic echocardiogram. Two of the 3 patients with valve replacements had vegetations only on their native valves. Of 11 patients with pure ischemic stroke, 4 received thrombolytics and had hemorrhagic conversion. Overall mortality of IES was 56% (10 of 18). Mortality in pure ischemic IES patients was 29% (2 of 7, median National Institute of Health Stroke Scale [NIHSS] 13) in those not receiving thrombolytics and 75% (3 of 4, median NIHSS 14) in those receiving thrombolytics. **Conclusions:** Though diagnosis of IE in the acute stroke setting is difficult, features of the history, examination, and laboratory data may raise concern for IE. In this case series, thrombolytics in patients with IE-associated stroke were associated with very poor outcomes.

Keywords

stroke (cerebrovascular disorders), central nervous system bacterial infections (infective endocarditis), intracranial hemorrhages, outcomes (techniques), thrombolysis

Introduction

Stroke is a complication of infective endocarditis (IE) in 21% to 40% of patients with IE.^{1,2} Cardiac valve vegetations embolize to the intracerebral arteries, causing acute ischemic stroke (AIS) with or without hemorrhage. Diagnosis of IE, based on the modified Duke criteria (Table 1),³ includes blood cultures and echocardiograms, making it difficult to distinguish IE-related stroke (IES) from other embolic stroke in the acute setting. This is an important distinction to make in the thrombolytic era because although 4 cases of IES treated with thrombolytics reported favorable outcome,⁴⁻⁷ intracranial hemorrhage (ICH) has been reported in 3 more patients.⁸ With so few reported cases, the overall safety of thrombolytics in IES is unknown and the American Heart Association guidelines are silent as to whether or not IE is a tissue plasminogen activator (tPA) contraindication.⁹ In this study, we identify clinical features helpful in early recognition of IES and describe outcomes following thrombolytic therapy.

Methods

Patients with AIS and IE were retrospectively identified through the prospectively populated University of Utah Hospital and Clinics stroke quality database that includes all cases of hospital presentation of stroke, by searching all cases with the field “endocarditis” checked. Data for this study were abstracted by original source document review. Fever was defined as temperature $>38^{\circ}\text{C}$. Classic stigmata of IE were considered present if mentioned. Infective endocarditis was classified as “definite” or “possible” based on the modified Duke criteria (Table 1). Follow-up imaging was performed

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Table 1. Modified Duke Criteria for Diagnosis of Infective Endocarditis^a

Major Criteria
1. Positive blood cultures for IE Typical microorganisms for IE from 2 separate blood cultures <i>Viridans streptococci</i> <i>Streptococcus bovis</i> , including nutritional variant strains HACEK group— <i>Haemophilus</i> spp, <i>Actinobacillus actinomycete comitans</i> , <i>Cardiobacterium hominis</i> , <i>Eikenella</i> spp, and <i>Kingella kingae</i> <i>Staphylococcus aureus</i> Community-acquired enterococci in the absence of a primary focus OR Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from: Blood cultures drawn more than 12 hours apart OR All of 3 or a majority of 4 or more separate blood cultures, with the first and last drawn at least 1 hour apart OR Single positive blood culture for <i>Coxiella burnetii</i> or antiphase I IgG antibody titer
2. Evidence of endocardial involvement Positive echocardiogram for IE TEE recommended in patients with prosthetic valves, rated at least “possible IE” by clinical criteria, or complicated IE (paravalvular abscess); TTE as first test in others Definition of positive echocardiogram Oscillating intracardiac mass, on valve or supporting structures, or in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation OR Abscess OR New partial dehiscence of prosthetic valve OR New valvular regurgitation—increase in or change in preexisting murmur not sufficient <i>Minor Criteria</i> <ol style="list-style-type: none"> 1. Predisposition—predisposing heart condition or intravenous drug use. 2. Fever—38.0°C (100.4°F). 3. Vascular phenomena—major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions 4. Immunologic phenomena—glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor 5. Microbiologic evidence—positive blood culture but not meeting major criterion as noted previously (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) OR serologic evidence of active infection with organism consistent with IE

Abbreviations: IE, infective endocarditis; IgG, immunoglobulin G; TEE, transesophageal echocardiogram.

^aA diagnosis of definite IE requires 2 major criteria, 1 major and 3 minor criteria, or 5 minor criteria. A diagnosis of possible IE requires 1 major and 1 minor criteria or 3 minor criteria.

1 to 8 days post-initial stroke presentation. Stroke severity was measured by the National Institute of Health Stroke Scale (NIHSS), with 4 recorded prospectively, 11 abstracted retrospectively using a validated method,¹⁰ and 3 lacking sufficient documentation to score. Clinical outcome was described by modified Rankin Scale (mRS) at hospital discharge or death and was retrospectively abstracted. Binomial variables are reported as frequencies, normal distributions are reported as mean \pm standard deviation, and skewed variables (age, NIHSS) are reported as median and interquartile range (IQR). Institutional Review Board approval and waiver of informed consent were obtained.

Results

From January 2001 to December 2007, there were 2830 cases of stroke (1801 AIS, 293 transient ischemic attack, 526 ICH, and 210 subarachnoid hemorrhage [SAH]). Of all, 22 cases were recorded as having endocarditis, with 18 meeting

modified Duke criteria (12 definite and 6 possible); these 18 were included for further analysis. Presenting stroke subtypes included 11 with pure ischemic stroke, 2 with ICH, and 5 with a combination of ischemia and SAH. In patients with pure ischemic stroke, the median initial NIHSS was 14 (IQR 8-14).

The most common IE-related findings on initial examination were fever and heart murmur (Table 2). Six patients (33%) had documented fever at presentation; an additional 5 (28%) reported subjective fever. In all, 8 (44%) had a heart murmur auscultated on initial evaluation, including 3 (17%) with a history of valve replacement. Only 3 (17%) had documented Janeway lesions and splinter hemorrhages, including 1 (6%) who also had Roth spots.

The most common initial laboratory abnormality was leukocytosis (11 patients, 61%). Of all, 10 (56%) presented with anemia and 6 (33%) with thrombocytopenia. Erythrocyte sedimentation rate (ESR) was elevated in 6 (60%) of 10 patients; C-reactive protein (CRP) was elevated in 4 (80%) of 5 patients.

Table 2. Clinical, Laboratory, and Imaging Findings^a

	n (%)
Demographics	
Female	9 (50)
Age (mean, SD)	56.6 (16.5)
Race/ethnicity:	
Non-Hispanic white	13 (72)
Hispanic white	2 (11)
Other	3 (18)
Initial physical examination	
Fever (>38°C)	6 (33)
Subjective fever prior to evaluation	5 (28)
Heart murmur	8 (44)
Janeway lesions	3 (17)
Splinter hemorrhages	3 (17)
Roth spots	1 (6)
Osler nodes	0 (0)
Initial laboratory results	
Leukocytosis (WBC range 11-25 k/μL)	11 (61)
Anemia (Hct range 24%-39%)	10 (56)
Thrombocytopenia (Plt range 93-125 k/μL)	6 (33)
Subsequent laboratory results	
Elevated ESR (n = 10)	6 (60)
Elevated CRP (n = 5)	4 (80)
Positive blood cultures	13 (72)
Echocardiogram	
Vegetation on TTE (n = 13)	5 (38)
Vegetation on TEE (n = 11)	11 (100)
Vegetation on TEE not seen on TTE in those with both studies (n = 8)	6 (75)
Vegetation on prosthetic valve (n = 3)	1 (33)
Angiography: CTA, MRA, conventional angiogram	
Mycotic aneurysm (n = 15)	1 (7)

Abbreviations: WBC, white blood cells; Hct, hematocrit; Plt, platelets; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram; CTA, computed tomography angiography; MRA magnetic resonance angiography.

^a Total number of patients is 18 unless otherwise noted.

Fifteen patients received vessel imaging: 5 with computed tomography angiography (CTA), 8 with magnetic resonance angiography (MRA), 1 with both CTA and MRA, and 7 with conventional angiography, 6 of whom had a preceding CTA or MRA. Only 1 patient had a mycotic aneurysm, which was identified by conventional angiography and not visualized by the preceding MRA.

All 18 patients underwent echocardiography; 16 (89%) had valvular vegetations. Thirteen patients underwent transthoracic echocardiogram (TTE); 5 (38%) showed vegetations (mitral valve in 4 and tricuspid valve in 1). Eleven patients underwent transesophageal echocardiogram (TEE) and all revealed vegetations (aortic valve in 3, mitral in 7, and both mitral and aortic in 1). Of the 8 patients with a negative TTE, 6 (75%) had a subsequent TEE demonstrating vegetations (mitral valve in 5 and aortic in 1). Of the 3 patients with valve replacements, only 1 had prosthetic valve vegetation; the remaining vegetations were on native valves.

All patients had blood cultures drawn, and 5 (28%) were negative. A wide variety of pathogens were identified in the positive cultures (Table 3).

Of the 11 patients with pure ischemic stroke, 5 presented within 6 hours, 1 of whom did not receive thrombolytic therapy due to suspected endocarditis. The remaining 4 patients who presented within 6 hours received intravenous (IV) or intra-arterial (IA) thrombolytics ± attempted mechanical clot retrieval (Table 3). All 4 patients developed ICH, which was demonstrated on follow-up imaging obtained 11 to 28 hours following intervention: 1 with hemorrhagic conversion (HC); 2 with a combination of HC, ICH in a new location, and SAH; and 1 with SAH and ICH. Three of 4 died, all within 2 weeks. The fourth had an mRS of 5 after inpatient rehabilitation.

Overall mortality of IES was 56% (10 of 18). Mortality in patients with pure ischemic stroke was 29% (2 of 7, median presenting NIHSS 13) in those not receiving thrombolytics and 75% (3 of 4, median presenting NIHSS 14) in those receiving thrombolytics.

Discussion

It is generally recognized that there is an increased risk of ICH in IES. Despite this, previous reports of thrombolytics in IES reflect variable outcomes. Single case reports of 2 adults with IES treated with IV-tPA had positive outcomes^{4,5} as did single case reports of an adult and child with IES treated with IA thrombolytics.^{6,7} However, in a case series of 3 adults with IES treated with IV-tPA, all 3 developed ICH and 1 died.⁸ Although the formation and rupture of mycotic aneurysms is a potential mechanism of ICH, and the patient in our series with a mycotic aneurysm presented with ICH, mycotic aneurysms have not been commonly reported in this case series or others.⁸ Additional possible mechanisms include septic emboli causing erosive arthritis with vessel rupture, immune complex-mediated arthritis, and infiltration of meningeal vasculature.^{11,12}

Our case series supports the known increased risk of ICH in IES: 67% of all our IES patients presented with or subsequently developed ICH. Additionally, all 4 patients with pure ischemic stroke receiving thrombolytics developed new ICH. Thus, it is imperative to recognize IE as a possible cause of stroke. However, in the short window for IV and IA tPA,⁹ the obvious difficulty of basing diagnosis of IE on the modified Duke criteria is that it relies heavily on test results not obtainable within hours of presentation. Physicians must therefore rely primarily on other factors to determine the likelihood of IE.

Three patients in this study had a history of valve replacement, but only 1 had a prosthetic valve vegetation, consistent with a report that neurological complications occur with the same frequency in native and prosthetic valve endocarditis.¹³ Therefore, a history of valve replacement in the absence of

Table 3. Stroke Subtypes, Severity, Pathogen, Intervention, and Outcomes

Patient #	Presenting Stroke Subtype			Initial NIHSS	Diagnosed IE at Stroke Presentation	Pathogen	Intervention	Follow-Up Imaging	Outcome (mRS)
	Ischemia	ICH	SAH						
1 ^a	X			15	No	<i>S viridans</i>	IV-tPA	HT (ICH)	5
2	X		X	4	Suspected	<i>S viridans</i>	None	Expected evolution	6
3 ^a	X			16	Suspected	<i>E faecalis</i>	None	Expected evolution	4
4	X			13	Yes	<i>P aeruginosa</i>	None	Expected evolution	6
5 ^a	X			14	No	<i>Coag-neg Staph</i>	IA-tPA, Merci	HT (ICH), SDH	6
6	X			1	Suspected	None identified	None	Not done	0
7	X			2	No	<i>S lugdunensis</i>	None	Not done	1
8	X		X	–	No	MSSA	None	New ischemia, HT (ICH + IVH)	5
9 ^a	X			8	No	<i>E faecalis</i>	IV-tPA	ICH, SAH	6
10 ^a	X			14	No	<i>E Faecalis</i>	IV-tPA, Merci	HT (ICH + IVH), SAH	6
11	X		X	14	No	None identified	None	New ischemia	6
12	X		X	20	Yes	None identified	None	Expected evolution	6
13 ^b	X		X	–	Yes	<i>Staphylococcus</i>	IA-tPA, angioplasty	Expected evolution	6
14	X			19	No	<i>Enterococcus</i>	None	Expected evolution	4
15		X		1	Yes	<i>S milleri</i>	None	SDH	1
16		X	X	–	No	MSSA	None	Expected evolution	6
17	X			14	Suspected	None identified	None	New ischemia, HT	6
18	X			9	No	MSSA	None	Expected evolution	4

Abbreviations: *Coag-neg Staph*, coagulase-negative Staphylococcus; *E faecalis*, *Enterococcus faecalis*; HT, hemorrhagic transformation; IA-tPA, intra-arterial tissue plasminogen activator; ICH, intracranial hemorrhage; IV-tPA, intravenous tissue plasminogen activator; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; MSSA, methicillin-sensitive *Staphylococcus aureus*; NIHSS, National Institute of Health Stroke Scale; *P aeruginosa*, *Pseudomonas aeruginosa*; *S lugdunensis*, *Staphylococcus lugdunensis*; *S milleri*, *Streptococcus milleri*; *S viridans*, *Streptococcus viridans*; SAH, subarachnoid hemorrhage; SDH, subdural hematoma.

^a Presented within 6 hours of stroke symptom onset.

^b This patient had known endocarditis and a minor SAH on presentation, but after discussion with the family and in the setting of a disabling left middle cerebral artery stroke, he received IA-tPA and angioplasty. This restored blood flow without worsening SAH on follow-up imaging, but he never regained consciousness and died 3 days later.

other IE clinical signs should not necessarily preclude thrombolytic therapy.

Although only 33% of the patients in this series were febrile on initial evaluation, an additional 28% were subjectively febrile prior to presentation. Patients' subjective reports of fever may be less reliable than objective fever on presentation but should not be discounted.

Heart murmur was documented in 44% of patients, and especially in a patient with no prior murmur history, is concerning for IE. Classic stigmata of IE such as Janeway lesions, splinter hemorrhages, and/or Roth spots were rarely identified (17%) but are valuable evidence for the presence of IE and can be quickly screened.

Leukocytosis and anemia, the most common laboratory abnormalities, are not specific to IE and must be considered in the clinical context. Both ESR and CRP may provide additional indications of IE but are not usually available within the thrombolytic window.

This case series supports the current recommendations that patients with "possible IE" by clinical criteria should have TEE without preceding TTE,³ since 75% of the patients with a normal TTE subsequently showed vegetations on TEE. However, echocardiography is not commonly available

acutely. Multislice CT may be able to detect aortic valve vegetation¹⁴ but has unknown sensitivity and specificity. Currently, no imaging technique can diagnose valvular vegetation within the time constraints of acute stroke management.

Limitations of this study include its retrospective design and single-center source of cases. As this is a small observational study, we could not control for potential confounders. For example, patients treated with thrombolytics presented earlier than those not treated. However, early presentation in the treated group would be expected to bias the group toward better outcomes, which we did not observe. In the future, a prospective multicenter registry could more accurately determine IES outcomes.

Conclusion

In our limited experience, patients with IES treated with thrombolytics have a high risk of hemorrhage, and favorable functional outcome is extremely uncommon regardless of treatment. In this retrospective case series, we found that a history of fever, heart murmur, IE stigmata, leukocytosis, and anemia should raise suspicion for IE in the acute stroke setting. Since the diagnosis of IE cannot be confirmed

definitively with blood cultures or echocardiography within the thrombolytic intervention time frame, clinicians must weigh the risk of thrombolysis in suspected IE against the potential benefit of thrombolysis in other causes of AIS.

Authors' Note

Dr Walker is the principal author. He conceptualized and designed the study, analyzed and interpreted the data, and was involved in the drafting and revising of the manuscript. Dr Sampson assisted in the conceptualization and design of the study as well as revising the manuscript for intellectual content. Dr Skalabrin assisted with conceptualization and design of the study as well as analysis and interpretation of the data. Dr Majersik assisted with analysis and interpretation of the data as well as revising the manuscript for intellectual content. Statistical analysis was completed by Drs Kevin A. Walker and Jennifer J. Majersik, both of whom are assistant professors of neurology in the Department of Neurology at the University of Utah.

Declaration of Conflicting Interests

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