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Incidence of neurological complications in patients with native-valve infective endocarditis and cerebral microembolism: an open cohort study

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Running title: Cerebral microembolism in infective endocarditis

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ABSTRACT

Background

The objective of this open cohort study was to assess the association between neurologic complications in patients with definite native-valve infective endocarditis (IE) and cerebral microembolism (MES). MES detection was performed with one-hour, bilateral middle cerebral arteries (MCA) insonation using a Transcranial Doppler ultrasound (TCD) machine.

Methods and results

Thirty patients with definite native-valve IE were stratified into two groups based upon the presence of MES. The most striking difference between the two groups of patients was the incidence of clinically evident neurologic complications. Neurologic complications of IE occurred in ten (83.3%) patients with positive MES and in six (33.3%) MES-negative patients (p=0.021). Ischemic stroke was the most common complication, occurring in eleven of sixteen patients, followed by meningitis in four patients and cerebritis in one patient. There was a trend towards greater in-hospital mortality in patients with recorded MES than MES negative, although this was not statistically significant (33.3% vs 16.6%; p=0.392).

Conclusions

Our results reveal a significant association between MES and neurologic complications in patients with native-valve infective endocarditis. TCD is a promising tool in predicting individual patient risk for neurological complications of IE.

BACKGROUND

Neurologic complications can occur in 21% to 56% of patients with infective endocarditis (IE) (1-6). Cerebral emboli, occurring in 42-62% of all these patients, can be particularly devastating. Early detection of a clinically benign variant known as cerebral microembolism may offer assistance in identifying a need for early cardiac surgery thus improving morbidity and mortality. They are also an indicator of an increased risk of stroke (7). Transcranial Doppler ultrasound (TCD) is a useful tool for the detection of microembolic material, both gaseous and solid, within intracranial cerebral arteries. Cerebral microemboli are recorded in up to 43% of patients with IE using TCD (7-9).

The most effective methods to prevent neurological complications and their severe consequences are early diagnosis and appropriate therapy of IE (1,3,10,11). Clinical studies demonstrate that early treatment significantly decreases the rate of embolic events (11,12,13).

The literature regarding cerebral microembolism and patients with IE is sparse. Prior studies often included small patient populations, limited data, short recording times, and one insonated MCA (8,9). One trial demonstrated that the sensitivity and specificity of microembolic signal (MES) recordings detection method in patients with potential cardiac sources of embolism (one artery insonation during 30 minutes recording) was 31% and 95% respectively (9).

The aim of this study was to assess the association between neurologic complications in patients with definite native-valve left-sided IE and cerebral microembolism detected by TCD using two 2-MHz probes and 60 minute recording time.

METHODS

Data collection

This prospective study was performed between January 2003 and December 2007 at the University Hospital for Infectious Diseases in Zagreb. The following parameters were recorded in a database: age, gender, physical and neurological signs, clinical outcome, echocardiography findings [transthoracic (TTE) and transesophageal (TEE) respectively], brain CT scan, antibiotic regimen, blood cultures, autopsy findings and microembolic signal (MES) recordings. Data was collected during the first 72 hours after admission to the hospital. Brain CT scans were performed on patients who developed neurologic complications.

Patients' selection

Adult (≥18 years) patients with a diagnosis of native-valve IE according to modified Duke's criteria were considered for TCD. Patients were excluded from the study if they had right-sided IE, prosthetic heart valve(s), other possible origin(s) of cerebral microembolism, temporal bone 'acoustic window' absence, or if treated with parenteral antibiotics for more than two weeks prior to TCD. Other possible etiologies of MES include: aortic arch atheroma, atrial fibrillation, atrial myxoma, dilated cardiomyopathy, left ventricular thrombus, mitral valve prolapse, mitral valve calcification and carotid artery plaques. MES recording in the prosthetic valve IE (PVIE) group was not valid as a predictive tool. These findings were previously found to be not specific (14). Patients were excluded if they demonstrated any neurological symptoms prior to the initiation of the study.

Definitions

Definite infective endocarditis was diagnosed according to modified Duke's criteria (15). The neurologic complications were divided into infectious (meningitis and brain abscess/cerebritis) and non-infectious (ischemic stroke and cerebral hemorrhage) complications. An ischemic stroke was diagnosed by the presence of a focal neurological

deficit that persisted over 24 hours in conjunction with a positive finding on the CT or MRI image. Cerebral hemorrhage was defined as intracranial bleeding in the setting of acute neurological change and a positive CT scan finding. The diagnosis of bacterial meningitis required neutrophilic pleocytosis (≥ 100 white cells/ml of CSF with more than 50% neutrophils), CSF-blood glucose ratio <0,4 and CSF protein concentration >0.450 g/l. The diagnosis of a brain abscess/cerebritis required radiologic features. Neurologic complications that occurred at any point during the disease course were considered associated with IE. According to the presence of microembolic signals (MES) the patients were stratified into 'MES positive' and 'MES negative' group. MES positive was defined as ≥ 1 microembolic signal within a one-hour record.

Transcranial Doppler ultrasound

TCD monitoring was performed by using a Multidop 4 X (DWL, Sipplingen, Germany) with two 2-MHz probes of 1.7 cm in diameter. The software used was TCD-8 for MDX, version 8.0 by Aaslid Rune.

The scale was set between 32-100 and +150 cm/s. The machine employed a 128-point fast Fourier transform (FFT) resolution, FFT length of 2 ms and FFT overlap of 60%. The high-pass filter was set at 100 Hz, detection threshold at 9 dB and the power was set at 70%. A sample volume of 5 mm in length and a low gain provided settings optimal for embolus discrimination from the background spectrum.

Both middle cerebral arteries (MCA) were insonated simultaneously through the temporal bone windows at a depth of 48-58 mm, according to standard criteria, for a period of 60 minutes (7,16). The probes were secured on the head of the patient with a specially designed spectacle frame, which assurred a constant angle of insonation. All MES were automatically recorded on a hard disk and later analyzed off-line by a manual operator. The following criteria were required in order to demonstrate MES: random occurrence, brief duration (0.1 second), high intensity (minimum 9 dB above background intensity), primary

unidirectional quality within the spectrum, and causing a spike in the power/intensity trace accompanied by an audible “chirp” or “pop”.

Statistical analysis

Univariate statistics included calculation of the mean values, standard deviations, median and interquartiles for continuous variables and frequencies for the categorical variables. Bivariate statistics assessed the differences between ‘MES positive’ and ‘MES negative’ groups. The Mann-Whitney test was used to estimate the difference amongst continuous variables. For categorical data, the chi-square and Fisher’s exact test were used. Data were analyzed using the ‘SAS 9.1’ software (SAS Institute Inc., Cary, NC).

RESULTS

102 patients with endocarditis were treated in our hospital during the 5-year period. TCD was successfully performed in thirty patients. Seventy-two patients were excluded from the study due to prosthetic-valve IE (16 patients), other known or possible origin of cerebral microembolism (13 patients), those with right-sided IE (14 patients), patients with prior history of parenteral antibiotic treatment more than two weeks before TCD (22 patients), patients without temporal bone ‘acoustic window’ (5 patients) and two patients who died of reasons not associated with infective endocarditis (hepatorenal syndrome and disseminated breast carcinoma, respectively). Thirty patients remained in the study to test the association between cerebral microembolism and neurologic complications. The basic cerebral hemodynamic parameters (mean blood flow velocities and pulsatility indexes) in all participating patients were within normal range. There were no patients with coagulopathies.

Baseline demographic data and characteristics of the patients with and without recorded MES are presented in Table 1. Microembolic signals were recorded in twelve of thirty patients with left-sided IE. The two groups did not differ in age or gender. Although there were more patients with an affected mitral valve in the MES-positive group (58.3% vs 33.3%), the difference was not statistically significant (p=0.328). Staphylococcal infections

were more common in patients with recorded MES, however there was no statistical difference. This is likely secondary to the small patient population (58.3% vs 27.7%, difference 31%, 95%CI 0 to 58%).

The sensitivity and specificity of the method was 83.3% and 85.7% respectively. Positive predictive value was 83.3% and the relative risk for neurological complication in MES positive patients was 2.50.

The most striking difference between the two groups of patients was the incidence of clinical neurologic complications. Neurologic complications of IE occurred in ten (83.3%) patients with positive MES and in six (33.3%) MES-negative patients (p=0.021). The most common non-infectious morbidity was ischemic stroke. It occurred in eleven of sixteen patients (68.7%). Infectious complications occurred in five of sixteen patients (31.2%) (bacterial meningitis in four patients and cerebritis in one patient). *Staphylococcus aureus* was the most common pathogen in patients with meningitis (three patients). *Moraxella lacunata* cerebritis was found in one patient with endocarditis.

The incidence of neurologic complications that developed after the start of antimicrobial treatment was 53.3% (16/30). The duration of treatment before the onset of symptoms ranged between 3-23 days (Table 2). In 68.7% (11/16) of these patients, the treatment course lasted ≤ 8 days. The etiology was secondary to staphylococcal infection in 50% of the patients and mitral valve lesions in 62.5% of patients.

Twelve patients with staphylococcal IE were included in study. Seven of these patients were MES positive and five patients were MES negative. In the MES positive group all patients developed neurological complications (7/7) compared with only one patient in the MES negative group (1/5; 20%).

Four patients in the MES positive group of staphylococcal IE were found to have large and mobile vegetations attached to the anterior mitral leaflet. One patient had involvement of the posterior mitral leaflet. The aortic valves were affected in two patients with vegetations. These measured 8×4 mm and 12x9 mm in size. The latter vegetation was found at the bicuspid valve accompanied by a paravalvular abscess that was 22×24 mm in

size. In the MES negative group of staphylococcal IE, the single patient who developed neurologic complications had an anterior mitral leaflet vegetation 12×3 mm in size. The echocardiography in the remaining patients revealed smaller or wide-base vegetations. A proportion of the patients were misclassified, particularly in non-staphylococcal IE group.

Neurological complications developed in 60% (3/5) of the MES positive and in 38.4% (5/13) of the MES negative, non-staphylococcal IE. This difference was less prominent in the affected valves: 87.5% (7/8) of the MES positive patients with mitral valve IE had a neurologic event compared with 75% (3/4) of the MES positive patients with non-mitral IE. Furthermore, MES negative groups with neurologic complications showed similar injury of the mitral valve (37.5% vs 30%).

Five patients underwent valvular surgery due to severe aortic (three patients) and mitral (two patients) regurgitation. One of these patients was MES positive (mitral valve IE) and four patients were MES negative. Ischemic stroke developed in two patients prior to surgery, one of whom was MES positive and another who was MES negative.

There were seven patients in MES positive group without indications for surgery (7/12; 58.3%). Six of these patients developed neurological complication (85.7%). The most common complication was meningitis (four patients) followed by cerebritis (one patient), and finally ischemic stroke (one patient).

Systemic embolizations were also more common among MES-positive patients (58.3% vs 16.6%; p=0.045). There was a trend towards greater in-hospital mortality in patients with recorded MES than MES negative, although this was not statistically significant (33.3% vs 16.6%; p=0.392). Five of sixteen patients with neurologic complications died compared to two out of fourteen patients without.

DISCUSSION

We found that the patients with native-valve IE with at least one MES detected by TCD are at greater risk for symptomatic neurologic complications. The combined use of both MCA insonation and extended time of MES recording increased the sensitivity of the method from 31% to 83.3% (9).

MES were found in 40% of the patients. Over 80% of these patients manifested neurologic complications. This was more common in comparison to patients with neurologic complications without recorded MES. The co-existence of MES and neurologic complications was commonly seen with mitral valve endocarditis and staphylococcal infections. This is similar to previous reports (7,11,12). Furthermore, the co-existence of cerebral and systemic embolization was also evident.

The high incidence of neurologic morbidity (53.3%) despite ongoing antimicrobial treatment is likely the result of short treatment duration, staphylococcal infection and frequent vegetations on mitral valve.

Our study has several limitations. One limitation is the small patient population, which resulted from the rigid exclusion criteria used to enhance the specificity of the study . This was done to assure the origin of emboli. The strict exclusion criteria may also result in selection bias. Due to the highly selective approach, the number of potential confounding variables was minimized making our results more reliable. The sensitivity and specificity of our method were both high, particularly in regards to infectious complications. Unfortunately, the method failed to predict an embolic stroke in a proportion of patients. A repeat examination would likely be beneficial by increasing the sensitivity of this method. Due to the small sample size and subsequent lack of statistical significance, we were unable to show that microembolizations are associated with greater mortality of IE despite the obvious trend toward poorer outcome.

Our results reveal a significant association between MES and neurological complications in patients with definite native-valve infective endocarditis. It appears that TCD is a promising tool for predicting individual patient risk for neurologic complications.

Larger studies are necessary to validate our findings. These studies will need to evaluate the combination MES with current risk characteristics of infective endocarditis to determine how MES can improve the predictive accuracy of existing risk stratification. Further studies should focus on the patients who do not have other indications for valvular surgery.

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Table 1. Baseline demographic data and characteristics of thirty patients with definite native-valve infective endocarditis

	all patients n=30	**MES*-positive group n=12**	**MES-negative group n=18**	**p**
age (years)				
mean±SD	54,5±17,6	53,8±19,8	54,9±16,6	0,932
median (interquartiles)	58 (43 - 69)	61,5 (38 - 68)	58 (43 - 69)	
gender				
male	17 (56,6%)	5 (41,6%)	12 (66,6%)	0,328
female	13 (43,3%)	7 (58,3%)	6 (33,3%)	
affected heart valve				
aortic	14 (46,6%)	4 (33,3%)	10 (55,5%)	0,411
mitral	13 (43,3%)	7 (58,3%)	6 (33,3 %)	0,328
both valve	3 (10%)	1 (8,3%)	2 (11,1%)	N/A
etiology				
S. aureus	10	5	5	
MRSA	2	2	0	
Str. bovis	1	0	1	
Str. intermedius	1	1	0	
Str. viridans	2	0	2	N/A
Str. agalactiae	2	2	0	
Group C Streptococcus	1	1	0	
Enterococcus faecalis	3	0	3	
Moraxella lacunata	1	0	1	
H. parainfluenzae	1	1	0	
Coxiella burnetti	1	0	1	
negative blood cultures/serology	5	0	5	
neurological complications	16/30 (53,3%)	10 (83,3%)	6 (33,3%)	0,020
non-infectious complications				
ischemic stroke	11/16 (68,7%)	6	5	
cerebral haemorrhage	0	0	0	N/A
infectious complications				
meningitis	4/16 (25%)	4	0	
brain abscess/cerebritis	1/16 (6,2%)	0	1	
systemic embolization	10 (33,3%)	7 (58,3%)	3 (16,6%)	0,045
mortality	23,3% (7/30)	33,3% (4/12)	16,6% (3/18)	0,391

Legend:

*MES = microembolic signal

Table 2. Characteristics of sixteen patients with native valve IE and neurological complications

No.	etiology	affected valve	MES* (Yes/No)	TCD♦ timing (duration of disease/treatment) - days	onset of neurological complication regarding to TCD♦ study - days	neurological complication	valve surgery (yes/no)	outcome
1	Str.intermedius	AML	Yes	13/7	2	meningitis	No	alive
2	S. aureus	MV	Yes	14/14	3	ischemic stroke	No	alive
3	S. aureus	AML	No	3/2	3	ischemic stroke	No	death
4	S. aureus	PML	Yes	6/3	1	meningitis	No	alive
5	S. aureus	AV	Yes	2/1	2	meningitis	No	death
6	S. aureus	AML and AV	Yes	10/3	7	ischemic stroke	No	death
7	S. aureus	AV	Yes	10/2	1	meningitis	Yes	alive
8	MRSA	AML	Yes	7/7	1	ischemic stroke	No	death
9	MRSA	AML	Yes	9/2	2	ischemic stroke	Yes	alive
10	Moraxella lacunata	PML	No	13/3	5	cerebritis	Yes	alive
11	Enterococcus faecalis	AV	No	14/5	18	ischemic stroke	No	alive
12	Str. agalactiae	AV	Yes	11/5	2	ischemic stroke	No	alive
13	Str. agalactiae	AML	Yes	4/2	2	ischemic stroke	No	alive
14	UKN	AV	No	14/7	6	ischemic stroke	No	alive
15	UKN	AML	No	10/4	1	ischemic stroke	Yes	alive
16	UKN	AV	No	12/5	7	ischemic stroke	No	death

Legend:

AV - aortic valve
MV - mitral valve
AML - anterior mitral leaflet
PML - posterior mitral leaflet
MES - microembolic signals
UKN - unknown
*MES = microembolic signal
♦TCD= Transcranial Doppler ultrasound