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Infective endocarditis with neurologic complications: 10-year experience

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The impact of neurologic complications on clinical outcomes in infective endocarditis was assessed. Medical records of patients with infective endocarditis from January 1, 1987 through September 30,1998 were analyzed. Patients were divided into two groups: one with neurological complications and the other without. The outcomes of the two groups were compared using Fisher's exact test. Fifty-eight patients fulfilled the definite Duke criteria. There were 46 men and 12 women, ranging from 3 to 71 years of age with a mean of 40.6 years. Pathogens of infective endocarditis were documented by blood culture in 55 (94.8%) of 58 patients as follows: 52 with gram-positive cocci, two with gram-negative bacilli, and one with fungus. All 58 patients had initially received antimicrobial agents. Eight (13.8%) of the 58 patients had received surgical valvular replacement because of medical treatment failure. Overall, 16 (27.6%) of 58 patients died. Neurologic complications were either the chief complaint or one of the major presenting symptoms in 16 (27.6%) of the 58 patients. Patients with neurologic complications had a higher mortality rate (50% vs 20.9%, $p = 0.025$) than those without neurologic complications. The adjusted risk ratio for neurologic complications for a fatal event was 3.51 (95% CI = 1.1-11.18, $p = 0.03$). Neurologic complications pose a significant problem in infective endocarditis. To reduce mortality, we recommend that more attention be paid to the treatment and prevention of the neurologic complications of infective endocarditis.

Key words: Infective endocarditis, mortality, neurologic complications

Infective endocarditis is the inflammation of the endocardium caused by microorganisms, which inciude bacteria, fungi, viruses, and parasites. Infective endocarditis has posed problems in diagnosis and treatment over the past decades. Although outcomes have improved, therapy for this infection is still not wholly satisfactory. The neurologic manifestation of infective endocarditis has a special picture [1]. However, there are few studies of the neurologic sequelae and outcomes of infective endocarditis patients in Taiwan [2-4]. This study aimed at investigating the impact of neurologic complications on the clinical outcomes.

Materials and Methods

A retrospective study of infective endocarditis was conducted by searching the computerized medical records of Changhua Christian Hospital from January 1, 1987 to September 30, 1998. During this period, members of the infectious disease unit (a cardiologist or a neurologist) assessed patients with a diagnosis of infective endocarditis. The following details were recorded: age, sex, date of admission, diagnosis of infective endocarditis, presence of risk factors (eg underlying heart disease, a mechanical prosthesis, a previons episode of infective endocarditis, any specific surgery or instrumentation, and intravenous drug addict), causative pathogens, echocardiographic findings, clinical features, and response to therapy. The clinical status of the patients at admission and during the subsequent hospital stay was assessed from the medical charts, and close attention was paid to neurologic manifestations. We recorded the echocardiographic findings, which include cardiac performance, pictures of cardiac valve, whole chordae tendineae, and perivalvular lesion. The major destructive valve was recorded if more than one valve was involved. Pathologic reports of infective endocarditis were available for all patients who had undergone surgery. All involved valves, known or suspected, were visualized. The annular areas were inspected for abscess. No autopsy was done during this period. According to the definite Duke criteria [5], the inclusion criteria contained at least one of the following: 1. Demon-stration of bacterial endocarditis at surgery; 2. Typical positive blood culture for infective endocarditis from two separate blood cultures and typical positive echocardiogram for infective endocarditis; and 3. One

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or more otherwise unexplained positive blood cultures in a patient with three of the following: predisposition, fever (body temperature > 38°C), vascular phenomena (major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracerebral hemorrhage, conjunctival hemorrhage, or Janeway lesion), immunology evidence (glomerulonephritis, Osler nodes, Roth spots, rheumatoid and echocardiography consistent with infective endocarditis.

Microbiological methods

Blood culture was performed in patients who were suspected to have infectious endocarditis. We used the BACTEC NR-860 system (Beckton Dickinson Diagnostic Instrument Systems, USA) for detecting pathogens. All *Staphylococcus aureus* and *Streptococcus* spp. were selected. *Staphylococcus epidermidis* was selected only if the same strain was isolated in culture of blood from two different sites from the same febrile patient, or if the isolate from blood was identical to that obtained by culture from central venous catheters and determined to be positive by the roll plate method with more than 15 colony-forming unit. We performed the procedure as the semiquantitative culture method [6]. All gram-negative pathogens that were isolated from blood were selected. Gram-positive and catalase-positive pathogens were identified by conventional biochemical tests, which include the latex agglutination kit (Pastorex Staph-Plus, Sanofi Fujirebio Diagnostic, Tokyo, Japan), coagulase tubing test (Coagulase plasma EDTA, Difco Laboratories, Detroit, MI, USA), 1% glucose fermentation test, and 5 μg-novobiocin disk (BBL, Sensi-Disc; Becton Dickinson, Cockeysville, MD, USA). Gram-positive and catalase-negative pathogens were identified by using conventional biochemical tests, which included a sensitized latex agglutination kit for grouping β-hemolysis streptococci (Slide Strepto-Kit, bio Merieux Vitek, Hazelwood, MO, USA), a commercial biochemical kit (the API-20 Strp kit, bio Merieux Vitek), and the Optochin test (BBL, Sensi-Disc; Becton Dickinson). Gram-negative pathogens were identified by conventional biochemical tests, which included a commercial biochemical kit (the API-20E kit, and the API-20NE kit, bio Merieux Vitek).

Neurologic manifestations

Clinical outcomes, especially the neurologic complications associated with infective endocarditis, were observed. We recorded any kind of neurologic complication (eg cerebral embolic infarction, mycotic aneurysm, intracerebral hemorrhage, subarachnoid hemorrhage, seizure, and meningitis). The results of neurologic diagnostic examination, which included brain computed tomography (CT) (GE, High Speed, Millwaukie, WI, USA), carotid angiography (GE, Advantx, DSA machine), and brain magnetic resonance imaging (MRI; 1.5-T MR system, Magnetom Symphony; Siemens, Erlangen, Germany) were recorded. Cerebrospinal fluid (CSF) findings were recorded. Patients were defined as the neurologic group with neurologic lesions if one or more of the following symptoms were observed during the course of infective endocarditis: 1. New objective neurologic abnormalities; 2. An abnormal CSF finding; and 3. Angiographic evidence of cerebral infarction, embolic occlusion of cerebral arteries, cerebral hemorrhage, cerebral mycotic aneurysm, or brain abscess. Complaints such as back pain, visual symptoms, psychiatric disturbances, and neuropathies were included only when verified by appropriate CSF data, radiographic studies, or the demonstration of new objective neurological findings.

Statistical analysis

The chi-square test and Fisher's exact test were used, when appropriate, to compare the categorical outcomes of the neurologic group and nonneurologic group. The significance level was set at $p = 0.05$. Risk ratios of potential risk factors were obtained by performing the Cox Proportional Hazard model analysis. A survival rate of up to 24 months was calculated by the Kaplan-Meier method and compared by log-rank test. All data were analyzed on a personal computer with SAS v6.12 software.

Results

In total 121 episodes of clinically diagnosed infective endocarditis in 114 patients were reviewed. Fifty-six patients were excluded because of incomplete medical records or not meeting the definite criteria. Fifty-eight patients, 46 (79.3%) men and 12 (20.6%) women (M/F ratio 4:1), fulfilled the definite Duke criteria, and they were then included in this study. Their ages ranged from 3 to 71 yeas with a mean age of 40.6 years. Predisposing heart diseases existed in 28 (48.2%) of the patients. Of the 58 patients, 50 (86.2%) had fever. Peripheral embolic phenomena, which include Jane-way lesion, Osler node, Roth spot, and petechiae (subconjunctival hemorrhage and splinter hemorrhage of the nail bed) were observed in 11 (19%) patients.

Among the 58 patients with infective endocarditis, 16 (27.6%) were identified as having neurologic complications. The neurologic findings were either the chief complaint or one of the major presenting symptoms. Disturbance in consciousness initially

Table 1. Neurologic complications of patients with infective endocarditis (n = 58)

Neurological event	No. of cases	%
Embolic infarction	10[a]	17.2
Cerebral hemorrhage	6[b]	10.3
Total	16	27.6

[a]Ten patients had cerebral embolic infarction, nine of whom had embolic infarction, one with both embolic infarction and seizure attack.

[b]Six patients had intracerebral hemorrhage, four of whom had both subarachnoid hemorrhage and intracerebral hemorrhage, two with intracerebral hemorrhage.

accounted for 50% (8/16) of cases, and focal weakness for 31.3% (5/16). Other major neurologic symptom included sudden onset of blurred vision in one patient, one with seizure, and uone with nsteady gait. Six of the 16 patients presented with headache, and four of these six patients were later diagnosed as having intracerebral hemorrhage.

Of the 58 patients, 47 (81%) had leukocytosis, and 45 (77.6%) had anemia on the day of admission. Erythrocyte sedimentation rate was elevated in 56 (96.6%) patients and C-reactive protein was elevated in 57 (98.3%) patients initially. Thirty-six patients had urine analysis performed, 13 (36.1%) of whom had hematuria. All of the 58 patients had received echocardiographic examinations; nine (15.5%) showed no vegetation whereas 49 (84.5%) showed vegetation on the cardiac valve. The involved cardiac valves were as follows: 31 (53.4 %) patients with mitral valve, 10 (17.2%) aortic valve, seven (12.1%) tricuspid valve, and one (1.7 %) pulmonary valve. Because of the neurologic symptoms and signs, 20 patients received brain CT, and two received brain MRI, one of whom received both brain CT and brain MRI. Of these 21 patients received imaging studies, 10 had embolic infarction and six intracerebral hemorrhage. Only one patient had undergone carotid angiography. Prominent veins of Labbe on the right side, but no other abnormal cerebral vascularity, were found. Three of the 58 patients had undergone a gallium scan to investigate fever, but no definitive abnormality was found.

Pathogens of infective endocarditis were documented in 55 (94.8%) of the 58 patients by blood culture: 32 with viridans streptococcus, two *Enterococcus* spp., one nutritional-variant *Streptococcus*, 11 methicillin-sensitive *S. aureus*, one methicillin-resistant *S. aureus*, five *S. epidermidis*, one *Serratia marcescens*, one *Pseudomonas aeruginosa*, and one fungus (one unidentified fungus in 1994). The two leading pathogens were viridans streptococcus and *S. aureus*. A similar mortality rate was found in patient with *S. aureus* endocarditis as compared with those of infective endocarditis caused by viridans streptococcus (23.5% vs 31.4%, $p = 0.747$).

All patients received antimicrobial therapy for 1 to 42 days (mean, 19 days). Penicillin and aminoglycoside were initially used, and the anti-microbial agents were later adjusted according to susceptibility test results. Eight (13.8%) patients received surgical valvular replacement in view of the poor response to medical treatment. Overall, 16 (27.6%) of the 58 patients died.

In this study, 42 (72.4%) of 58 patients had developed complications associated with infective endocarditis. Table 1 shows the neurologic complications of infective endocarditis. Sixteen patients had neurologic complications, 10 of whom had embolic infarction (nine with embolic infarction and one with both embolic infarction and seizure attack), six had intracerebral hemorrhage (four with both subarachnoid hemorrhage and intracerebral hemorrhage, and another two with intracerebral hemorrhage). Of these 16 patients, four had diabetes mellitus and five showed leukocytosis at initial admission. Table 2 shows the association of neurologic complications and bacteriology. Lumbar puncture was performed in five of the 16 patients (Table 3). Table 3 showed that four patients had pleocytosis in the CSF. All of the CSFs were aseptic.

Eight of these 16 patients died. The mortality was significantly associated with neurologic complications. Patients with neurologic complications had a higher mortality rate (50% vs 20.9%, $p = 0.025$) than those without neurologic complications. The mortality rate in the *S. aureus* group was not significantly higher than

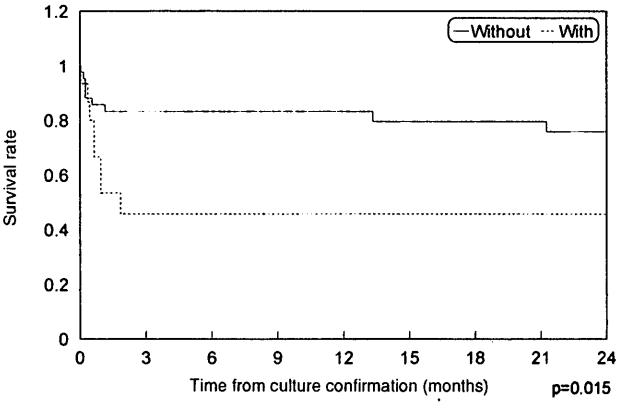

Fig. 1. Survival table by the Kaplan-Meier metod.

Table 2. Pathogens in infective endocarditis (n = 58)

Microorganism	No. of isolates (%)	Neurologic complications[a]
Methicillin-sensitive *S. aureus*	11 (18.9)	4
Methicillin-resistant *S. aureus*	1 (1.7)	0
Staphylococcus epidermidis	5 (8.6)	3
Viridans streptococci	32 (55.2)	8
Nutritional-variant *Streptococcus*	1 (1.7)	0
Enterococcus spp.	2 (3.4)	0
P. aeruginosa	1 (1.7)	0
S. marcescens	1 (1.7)	0
Fungus[b]	1 (1.7)	0
No growth	3 (5.2)	1
Total	58 (100)	16

[a]Neurologic complications: those infective endocarditis patients who had developed neurologic complications (such as embolic infarction, cerebral hemorrhage, subarachnoid hemorrhage, meningitis, and seizure).
[b]One unidentified fungus, in 1994.

Table 3. Findings of CSF in the five patients who underwent lumbar puncture

Case no.	Case 1	Case 2	Case 3	Case 4	Case 5
Demography					
Age (years)	45	60	5	41	12
Sex	Male	Male	Male	Male	Male
Clinical manifestations					
Causative pathogen	VS	Negative	VS	VS	MSSA
Site of culture	Blood	Blood	Blood	Blood	Blood
Involved valve	MV	MV	MV	MV	AV
Neurologic complication	E	E	E	E	E
Outcome	Survived	Died	Died	Survived	Died
CSF findings					
RBC (/mm^3)	0	5	63	7200[a]	3
WBC (/mm^3)	10	8	4	28	121
N/L	2/8	1/7	0/4	6/22	68/23
Protein (mg/dL)	48	55	81	45	33
Sugar (mg/dL)	48	178	64	88	NA
CSF Gram's stain	NF	NF	NF	NF	NF
CSF culture	NG	NG	NG	NG	NG

Abbreviations: VS = viridans streptococci; MSSA = methicillin-susceptible *S. aureus*; MV = mitral valve; AV = aortic valve; E = embolic infarction; NA = data not available; NF = not found; NG = no growth
[a]A traumatic tapping.

that of the viridans streptococcus group (23.5% vs 31.4%, $p = 0.747$).

Figure 1 shows the 24-month survival rate in each subgroup for various potential risk factors. Among these factors, patients with and without neurologic complication showed a significant difference in survival. Cox Proportional Hazard model analysis revealed that heart and neurologic complication are the most important indicators of the prognosis, with risk ratios of 3.51 (95% CI = 1.1-1.18, $p = 0.03$) and 3.21 (95% CI = 1.04-9.97, $p = 0.04$), respectively for a fatal event, after adjusting for age, sex, bacteria, and adequacy of medication.

Discussion

The traditional therapy for infective endocarditis has concentrated on the bacteriologic cure of the infected heart valve and the surgical correction of cardiovascular hemodynamic decompensation. Nowadays we pay more attention to dealing with the neurologic complications of infective endocarditis to decrease the morbidity and mortality. In Taiwan, few reports on the neurologic complications of infective endocarditis and the morbidity and mortality rate associated with neurologic sequelae are documented [2-4]. This study investigated the impact of neurologic complications on clinical outcomes of infective endocarditis.

In this study, 16 (27.6%) of the 58 patients had neurologic complications, 10 of whom had an embolic infarction, and six had an intracerebral hemorrhage. The incidence of neurologic complications ranged from 9% to 80% [7]. The clinical outcomes of neurologic complications associated with infective endocarditis, however, are more important than the incidence. We found that patients with neurologic complications had a significantly higher mortality rate than those without (50% vs 20.9%, $p = 0.025$), which was consistent with previous literature [8] . Jones *et al* [9] found that the mortality rate among patients with neurologic complications was 1.6 times greater than expected with infective endocarditis. Similarly, Harrison *et al* [10] noted a mortality rate of 67% in 33 patients with neurologic complications, contrasted with 44% in 83 patients without nervous system involvement. Lumbar puncture was performed in five of 16 patients, four of whom had pleocytosis in the CSF. All of the CSFs were aseptic. The reason for a negative result of CSF culture might be the previous usage of antimicrobial agents. No particular neurologic event was associated with specific CSF findings. Priutt *et al* [7] described a good correlation between CSF findings and the nature of the infecting organism. The case number is too small in this study to draw a definite conclusions.

In this study, the age, sex, and proportion of cases with rheumatic heart disease were comparable for the infective endocarditis patients with and without complication. Pruitt *et al* [7] found that virulent organisms, particularly *S. aureus* and enteric gram-negative bacilli, were common in patients with neurologic complications. The mortality rate in the *S. aureus* group, however, was not significantly higher than that in the streptococcus group (23.5% vs 31.4%, $p = 0.747$). Our result differs from that of Puitt *et al*'s study because of both a small case number and a different population.

Neurologic complications remain a critical problem in infective endocarditis. Of the 16 patients who had neurologic complications, 10 had embolic infarction and six intracerebral hemorrhage. The initial diagnosis was not always infective endocarditis, but a primary neurologic illness or some systemic diseases. Eight (50%) of the 16 patients died of neurologic complications. In contrast, the overall mortality rate was only 25.9% among those with infective endocarditis [3]. Of the neurologic complications, cerebral embolic infarction (62.5%) was the most frequent and important complication. Embolic infarction occurred in 10 patients, and two (20%) of them died later.

Many intracerebral mycotic aneurysms are asymptomatic until rupture occurs. Rupture is usually a catastrophic event with a fatality rate of 80% [7], and can produce subarachnoid hemorrhage, intraventricular hemorrhage, or direct intracerebral destruction of the brain. In this study, there were 10 patients with embolic infarction and six with intracerebral hemorrhage. Only one patient had received a carotid angiography, and this showed prominent veins of Labbe on the right side but no abnormal cerebral vascularity. At present CT scan or MRI of the brain cannot exclude infective aneurysm, nor does functional MRI can. Although there were no definitive neurologic abnormalities, serial follow-up of the aneurysm by angiography, CT scan, or MRI was still recommended by Almadi *et al* [11] despite that it is not cost-effective. We agree that routine CT scan and four-vessel angiography should be performed in any patient with infective endocarditis who develops any neurologic deficit [12]. Three of 58 patients underwent Gallium scan for fever survey, but serial follow-up of these three patient was lacking.

The functional outcomes of patients surviving neurologic complications, which include rupture of an intracerebral infective aneurysm, are not well documented. Bohmfalk *et al* [13], in his study of 19 survivors of ruptured infective aneurysms, defined outcomes as either partially recovered or completely recovered; whereas Frazee *et al* [14], in his series of seven survivors defined outcomes as normal or disabled. This study followed up patients for 24 months and shows that neurologic complications (OR = 3.21, 95% CI = 1.04-9.97, $p = 0.04$) are the most important factor for a poor prognosis of infective endocarditis. By calculating the 24-month survival rate in each subgroup for various potential risk factors and using Cox Proportional Hazard model analysis, we have shown that both heart and neurologic complications are the most important indicators of the prognosis, with risk ratios of 3.51 and 3.21, respectively for a fatal event, after adjusting for age, sex, bacteria, and adequacy of medication.

Neurologic complications cause a higher mortality rate in infective endocarditis, hence more aggressive intervention may be beneficial for these patients.

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