

Stroke Associated with Infective Endocarditis. Frequency and Prognostic Implications

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Article history

Received: 13-04-2021

Revised: 19-07-2021

Accepted: 31-07-2021

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Abstract: Stroke can be one of the most severe complications of Infective Endocarditis (IE) and it happens in 14% of patients with IE. Therefore, we aimed to review stroke frequency in patients diagnosed with IE in our hospital from 2010 to 2020. We defined it as IE-Associated Stroke (IEAS) when the stroke happened one month before or after IE's diagnosis. Sixty-six patients were diagnosed with IE during this period time and 15 (22%) suffered IEAS: 13 ischemic strokes, one Subarachnoid Hemorrhage (SAH) and one parenchymal hemorrhage with SAH. Patients with IEAS were more frequently men (80% vs 51% $p = 0.042$) and had less atrial fibrillation (13.3% vs 37.3%, $p = 0.071$). Although not statistically significant, *Streptococcus* sp (53% vs. 44.9%) and *Staphylococcus aureus* (33.3% vs. 16.3%) were more frequent in patients with IEAS. Mortality was increased in patients with IEAS (60% vs 13.7%, $p = 0.001$) especially in patients where stroke diagnosis was posterior to IE (88.9% vs 16.7%, $p = 0.011$). Hypertension (93.8% vs 63%, $p = 0.013$) and diabetes (53.2% vs 30%, $p = 0.052$) were also more frequent in those patients who died. In multivariate analysis, hypertension (OR 13.7 95% CI 1.4-138.4) and IEAS (OR 12.8 95% CI 2.8-58) were independently associated with death. The frequency of IEAS in our patients is comparable to what has been described in the literature. IEAS was associated with increased mortality.

Keywords: Infectious Endocarditis, Ischemic Stroke, Hemorrhagic Stroke

Introduction

It has gone more than a century since Sir William Osler made the first exhaustive description of Infective Endocarditis (IE) (Levy, 1985) in the XIX century. However, despite the advances in diagnosis and treatment, IE remains a clinical challenge nowadays. Moreover, the complexity of IE makes it necessary to set multidisciplinary "endocarditis teams" as has been recommended by the European Cardiology Society in a consensus statement in 2015 (Habib *et al.*, 2015).

In high-income countries an increasingly older population and the associated comorbidities are major determinants for the development of IE. In addition, degenerative valvular disease, prosthetic valves, intracardiac implantable devices and invasive medical procedures also play a role in developing IE. However, in low-middle income countries, rheumatic heart disease and congenital heart diseases still remain the most important factors (Cahill and Prendergast, 2016; Murdoch *et al.*, 2009; Njuguna *et al.*, 2017).

IE is diagnosed with the modified Duke criteria as definite, possible and rejected (Li *et al.*, 2000). Vascular

events, such as major arterial emboli, mycotic aneurysms and intracranial hemorrhages, are included in IE's diagnosis's minor criteria. In this setting, stroke can appear as an extracardiac complication of IE in 14% of the cases (García-Cabrera *et al.*, 2013) and usually carries a poor clinical prognosis (García-Cabrera *et al.*, 2013; Thuny *et al.*, 2007; Morris *et al.*, 2014).

Table 1: Microbiologic etiology in patients with IE

Microorganism	Frequency (%)	
	Europe	North America
<i>Streptococcus</i>	31	17
<i>Staphylococcus aureus</i>	28	43
CoNS	13	12
<i>Enterococcus</i>	9	13
Fungal	1	3
HACEK	2	0
Polymicrobial	1	1
Culture negative	10	7
Other	5	4

Adapted from Murdoch *et al.* (2009). CoNS, coagulase-negative staphylococci; HACEK, *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* spp.; VGS, viridans group streptococci

Meningitis, encephalopathy, seizures and cerebral abscess are other well-known complications of IE (Cahill and Prendergast, 2016; Hoen and Duval, 2013; Heiro *et al.*, 2000; Bashore *et al.*, 2006; Jones and Siekert, 1989; Greenlee and Mandell, 1973). Accordingly, neurology specialists may be involved and play an essential role in managing patients with IE.

The causal agents of IE are varied, in Table 1 we mentioned the most frequently involved.

Our study aimed to describe stroke frequency during the last ten years in patients diagnosed with IE in our hospital and describe the main clinical characteristics and prognostic implications.

Methods

Moisés Broggi Hospital is located in Barcelona's south metropolitan area and attends a population of 422.000 inhabitants. We selected from our local electronic records patients that had been diagnosed with IE (ICD-10 code I33) and ischemic stroke (ICD-10 codes I63), hemorrhagic stroke (ICD-10 codes I61), or subarachnoid hemorrhage (SAH, ICD-10 codes I60). Finally, we defined IE-associated stroke (IEAS) when stroke happened one month before or after IE diagnosis. We collected the following variables: age, sex, hypertension, diabetes, dyslipidemia, Chronic Kidney Disease (CKD), Ischemic Heart Disease (IHD), Atrial Fibrillation (AF), presence of Implantable Cardiac Devices (ICD), affected valve, microorganism causing IE, valve replacement surgery, the temporal relationship between stroke and IE diagnosis and death. Patients diagnosed with IE were divided into IEAS (IEAS+) patients and those without IEAS (IEAS-).

Statistical analysis was performed with IBM SPSS 26. Firstly, we compared patients with and without IEAS. Secondly, we selected those patients with IEAS and compared those in which stroke diagnosis preceded the diagnosis of IE and those with a stroke posterior to IE diagnosis. Continuous variables were described as means and Standard Deviations (SD) and categorical variables were expressed as percentages. Frequency tables were analyzed using Pearson's chi-squared test or Fisher's test, as appropriate. Quantitative differences between groups were compared using Student's t-test, ANOVA, or Mann-Whitney U test, as appropriate. We considered as statistically significant p values of <0.05 and all hypotheses were two-sided. When required, we used multivariate analysis to adjust for confounding variables.

Results

Sixty-six patients were diagnosed with IE in our hospital from 2010 to 2020. The main demographic and clinical characteristics are described in Table 2. Fifteen patients (22.7%) suffered an IEAS: 13 ischemic strokes, one Subarachnoid Hemorrhage (SAH) and one parenchymal bleeding with SAH. In addition, the patient with an isolated SAH underwent a brain angiogram and was diagnosed with a mycotic aneurysm (Fig. 1).

The middle cerebral artery was the arterial territory most frequently involved in patients with ischemic stroke and 10 out of 13 (77%) patients with ischemic stroke had acute ischemic lesions in more than one arterial territory, suggesting the embolic nature.

Stroke preceded the diagnosis of IE in 6 patients (42%). Detailed characteristics of patients with IEAS appear in Table 3.

Table 2: Basal characteristics of the 66 patients diagnosed with IE

	All patients (N = 66)	IEAS + (n = 15)	IEAS - (n = 51)	p value
Age, mean (SD)	69.06 (13.8)	69.9 (13.5)	66.13 (14.9)	NS
Sex, male, %	57.6	51	80	0.042
Hypertension, %	69.7	68.6	73.3	NS
Diabetes, %	36.4	37.3	33.3	NS
Dyslipidemia, %	51.5	49	60	NS
CKD,%	18.2	17.6	20	NS
IHD,%	13.6	11.8	20	NS
Atrial fibrillation,%	31.8	37.3	13.3	NS
ICD,%	3	2	6.7	NS
Valve, %				
Aortic	34.8	31.4	46.7	NS
Mitral	43.9	45.1	40	
Mitral and Aortic	13.6	13.7	13.3	
Tricuspid	4.5	5.9	NA	
Prosthetic valve, %	12.1	9.8	20	NS
Microorganism, %				
Staphylococcus aureus	20.3	16.3	33.3	NS
Non-aureus Staphylococcus sp	10.9	14.3	0	
Streptococcus sp	46.9	44.9	53	
Enterococcus Sp	21.9	24.5	13.3	
Valve replacement surgery, %	22.7	25.5	13.3	NS
Death, %	24.2	13.7	60	0.001

Abbreviations: CKD: Chronic Kidney Disease, IHD: Ischemic Heart Disease, ICD: Implantable Cardiac Device, IEAS: Infective Endocarditis Associated Stroke, NA: not applicable, NS: not significant

Table 3: Demographic characteristics of patients with stroke and IE

Patient N°	Age	Sex	Affected Valve	Microorganism	Stroke subtype	Location	IE debut with stroke	Time from IE to stroke	Death
1	89	F	Aortic-Mitral	S. Viridans	IS	L-MCA	Yes	NA	No
2	80	F	Mitral	S. Bovis	IS	L and R-MCA, L and R-PCA	No	15 days	Yes
3	80	F	Mitral	S. Viridans	IS	L-MCA, L-PCA	No	1 month	Yes
4	86	M	Aortic	S. Salivarius	IS	L and R-MCA, brainstem	No	21 days	Yes
5	71	M	Prosthetic Mechanical Aortic	E. Faecalis	IS	SCA	Yes	NA	No
6	66	M	Prosthetic Biological mitral	MRSA	IS	L and R-MCA;brainstem	Yes	NA	Yes
7	72	M	Prosthetic Biological Aortic	S. Gallolyticus	HS/SAH	Basal ganglia	No	26 days	Yes
8	62	M	Aortic	S. Oralis	IS	Brainstem	Yes	NA	No
9	51	M	Aortic-Mitral	E. Faecalis	SAH	Mycotic aneurism-L-MCA	No	8 days	Yes
10	63	M	Mitral	S. Aureus	IS	L and R-MCA	No	10 days	Yes
11	47	M	Aortic	S. Aureus	IS	L and R-MCA, L and R-PCA	No	3 days	Yes
12	49	M	Aortic	S. Aureus	IS	L and R-MCA, L and R-PCA	Yes	NA	No
13	80	M	Aortic	S. Epidermidis	IS	L and R-MCA; R-PICA	No	5 days	Yes
14	47	M	Mitral	S. Aureus	IS	L and R-MCA	Yes	NA	No
15	49	M	Mitral	S. Oralis	IS	L and R-MCA; R-PICA	No	3 weeks	No

Abbreviations: IS: Ischemic stroke; HS: hemorrhagic stroke; L: left, R: Right, MCA: Middle cerebral artery; PCA: Posterior cerebral artery; SCA: Superior cerebellar artery; SAH: Subarachnoid hemorrhage; PICA: Postero inferior cerebellar artery, NA: Not applicable.



Fig. 1: A 51 years old male with Mitro-Aortic IE complicated with hemorrhagic stroke due to a mycotic aneurism. A. Basal CT showing subarachnoid hemorrhage (red arrow). B. Mycotic aneurysm in a distal ramification of the MCA (green arrow). C: Coil implanted in the mycotic aneurysm (yellow arrow)

Patients with IEAS were more frequently men (80% vs 51% $p = 0.042$) and had less atrial fibrillation (13.3% vs 37.3%, $p = 0.071$). *Streptococcus* sp. (53% vs. 44.9%) and *Staphylococcus aureus* (33.3% vs. 16.3%) were more frequent in patients with IEAS, although the difference was not statistically significant. Mortality was markedly increased in patients with IEAS (60% vs. 13.7%, $p = 0.001$), especially in those with stroke posterior to IE diagnosis (88.9% vs. 16.7% $p = 0.011$). Hypertension (93.8% vs 63%, $p = 0.013$) and diabetes (53.2% vs 30%, $p = 0.052$) were also more frequent in those patients who died. In multivariate analysis, hypertension (OR 13.7 95% CI 1.4-138.4) and IEAS (OR 12.8 95% CI 2.8-58) were independently associated with death.

Discussion

The incidence of IE is 3-9 cases per 100,000 per year (Cao *et al.*, 2018; Hoen and Duval, 2013) and it has been stable over last decades, despite the advance of preventive medicine strategies and better diagnostics tools (Hoen and Duval, 2013; Murdoch *et al.*, 2009). Stroke in the IE

setting is infrequent (percentages can vary from 10-50% for embolic events, 65% affecting the central nervous system) (Heiro *et al.*, 2000; Morris *et al.*, 2014) but carries an ominous prognosis. For example, in our series of patients with IE for ten years, stroke appears as a complication of IE in 22.7%. This percentage is similar to previously reported (Thuny *et al.*, 2007; Sotero *et al.*, 2019; Anderson *et al.*, 2003; Fabri Jr *et al.*, 2006; Barsic *et al.*, 2013; Hasbun *et al.*, 2003), but it might be even higher since the risk of stroke remains increased in the first year after the IE diagnosis (Merkler *et al.*, 2015; Østergaard *et al.*, 2019). The observed mortality in our series is also comparable to other studies (García-Cabrera *et al.*, 2013; Anderson *et al.*, 2003; Hasbun *et al.*, 2003; Hobohm *et al.*, 2016).

However, Dickerman *et al.* (2007) showed us that the stroke rate during the first week of antibiotic therapy was 4.82 of 1000 patient-days. Still, this rate fell by 65% in the second week of treatment to 1.71 of 1000 patient days ($p < 0.001$) and continued constantly falling after the start of antibiotic therapy. This could be explained by the breakdown of the vegetation formed by inflammatory cells, endothelial cells, invading microorganisms, platelets and red blood cells

with antimicrobial therapy, leading to a decrease in the vegetation's size and or stabilization.

We defined IEAS when the stroke happened either one month before or after the IE diagnosis because the risk is maximal during this period and more likely a causative relationship with IE. Compared to other studies, we found a similar pattern of microorganisms and valvular involvement (Hoen and Duval, 2013; Bashore *et al.*, 2006; Hobohm *et al.*, 2016; Lee *et al.*, 2014), being *S. aureus* the most common single microorganism responsible for IE. This phenomenon is related to the increased healthcare contact in the general population and the chronification of diseases (Cahill and Prendergast, 2016; Bashore *et al.*, 2006; Jones Jr and Siekert, 1989; Greenlee and Mandell, 1973; Murdoch *et al.*, 2009), but possibly *Streptococcus sp.* still represents the foremost responsible for IE in the low and middle-income countries with a progressive increment of *S. aureus* infection (Cahill and Prendergast, 2016; Njuguna *et al.*, 2017). Similarly, we also found the classical multi-territorial involvement described for ischemic stroke caused by IE (Jones Jr and Siekert, 1989; Greenlee and Mandell, 1973; Lee *et al.*, 2014; Singhal *et al.*, 2002), being the middle cerebral artery the most affected territory. In fact, 3 of our patients with ischemic stroke before IE diagnosis had a single territorial infarct. Lee *et al.* (2014; Singhal *et al.*, 2002) described four patterns of ischemic lesions in DWI MRI (A) single lesion, (B) territorial infarction, (C) disseminated punctate lesions and (D) numerous small (<10 mm) and medium (10 to 30 mm) or large (>30 mm) lesions in multiple territories. It's crucial to highlight that only pattern D was exhibited in Non-Bacterial Thrombotic Endocarditis (NBTE) patients. Therefore, although brain imaging can show different patterns suggestive of an underlying IE, other clinical features such as fever, raised acute phase reactants or the presence of a new cardiac murmur must be taken into account.

The main result of our study is that stroke is associated with significantly increased mortality in patients with IE, especially when IE diagnosis preceded the stroke. Similar findings were reported by Epaulard *et al.* (2009). In a small study with 32 patients with IE, mortality was higher in patients with stroke after IE diagnosis (Murdoch *et al.*, 2009). Patients with acute stroke had probably been admitted to stroke units, with early neuroimaging and cardiac workout that had allowed an earlier detection and treatment of IE. However, the difference in mortality between patients diagnosed with stroke before or after IE should be confirmed with a larger sample. This association of IEAS with mortality was independent of hypertension, another factor associated with increased mortality and probably the fatal evolution might be caused by stroke occurrence.

This study has significant limitations; apart from the limited number of patients and its retrospective nature, we cannot assure that the patients had been treated with

coordinated protocols. This might impact mortality, for instance, the lack of cardiac surgery service inwards. However, we think that the important difference in mortality between both groups makes this point unlikely. Another caveat is that only patients with focal neurological signs were evaluated by a neurologist and went under a selection bias neuroimaging. It's well known that silent ischemic lesions are detected with routine neuroimaging, preferably cerebral MRI, but the ideal time and clinical relevance are still unknown and need further evaluation.

In conclusion, Stroke is an infrequent but serious complication of IE, associated with a high mortality, especially when stroke happens after IE diagnosis. The causing microorganisms are similar to previous series. A high grade of clinical suspicion and early diagnosis of IE might help to improve clinical prognosis in these patients.

Acknowledgement

We thank Jordi Vericat for his technical assistance.

Author's Contributions

Juan José Mengual Chirife: Collected the data and drafted the manuscript.

Manuel Gómez-Choco: Carried out the statistical analysis and drafted the manuscript.

Ester Moral: Designed the study and made a critical review of the manuscript.

Ethics

The investigation conforms to the principles outlined in the declaration of Helsinki. The need for written informed consent was waived for the retrospective character of the study.

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