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INFECTIVE ENDOCARDITIS (IE) FIRST DIAGNOSED AT AUTOPSY: ANALYSIS OF 31 CASES IN RIBEIRÃO PRETO, BRAZIL

Luiz Tadeu M. FIGUEIREDO, Everaldo RUIZ-JUNIOR & Tarciso SCHIRMBECK

SUMMARY

Thirty one infective endocarditis (IE) fatal cases whose diagnosis was first obtained at autopsy were studied. The clinical data of these patients (Group 1) showed significant differences compared to other 141 IE cases (Group 2). The average age of 53 years in Group 1 patients was 18 years higher than that of Group 2. The Group 1 patients had a low frequency of IE predisposing heart disease. Both patient groups presented fever (about 87%), but a significant low frequency of cardiac murmur (25.8%) was observed in Group 1 patients and echocardiography tests were performed in only 16.1%, suggesting that IE diagnosis was not suspected. Likewise, although most Group 1 patients appeared with severe acute illness, they did not present the classic IE clinical presentation. Blood cultures were performed in only 64.5% of the Group 1 patients. However, bacteria were isolated in 70% of these blood cultures and *Staphylococcus aureus* was isolated in 71.4%. The bacteria attacked mitral and aortic valves. Complications such as embolizations and cardiac failure occurred in almost half of the cases and they also presented with infections of the lungs, urinary tract, and central nervous system. Medical procedures were performed in practically all fatal cases whose diagnosis was first obtained at autopsy. Sepsis occurred in about half of the patients and it was followed by shock in more than 25%. This form of IE must be suspected in mature and in old febrile hospitalized patients having infection predisposing diseases, embolization, and suffering medical procedures.

KEYWORDS: Fatal infective endocarditis.

INTRODUCTION

Infective endocarditis (IE) is a serious disease whose mortality has been reduced in the last years and presently, in developed countries, decreased to levels of 23 or 19 %^{4,10}. The diagnostic confirmation of IE is traditionally done by isolation of the infecting microorganism in blood cultures and by sonographical evidence of endocardic vegetation. Due to great difficulties on uniformizing IE diagnosis, criteria have been defined to account for clinical, echocardiographic and pathological aspects. One of these is the Duke criteria which is used in several studies that confirm their suitable sensitivity and specificity^{1,4,5,6,7}.

In a study carried out in Ribeirão Preto, SP, Brazil, 180 episodes of IE occurred in 168 patients through 1992 to 1997, were analyzed⁹. Echocardiogram was done in 132 episodes of IE diagnosing IE in 111 of the exam tested patients. The mitral valve was attacked in 55, tricuspid in 30 and aortic, in 28 episodes of IE. Blood cultures were done in 148 episodes of IE cases. *Staphylococcus aureus* was isolated in 46 and *Streptococcus viridans* in 27 of the blood culture tested patients. Since a high frequency of sepsis was observed among the patients, the case fatality rate was 40.5%. Many fatal cases had the diagnosis first obtained at autopsy. Despite of the general profile of IE similar to that observed in developed countries, the high mortality rate observed was not in

accordance with the progresses in diagnosis and treatment of IE. The present study has been carried out in order to detect particular characteristics of the IE fatal cases whose diagnosis was first obtained at autopsy.

MATERIAL AND METHODS

Following the Duke criteria, 180 instances fulfilled a definite or a probable IE diagnostic, and were included in this study¹. All the patients were assisted in the general hospital of the School of Medicine of Ribeirão Preto, through 1992 to 1997. The clinical data of 31 fatal cases whose diagnosis was first obtained at autopsy (Group 1) were analyzed and compared to the data collected of the other 149 cases of IE (Group 2). Proportions were compared using the chi-square test ($p < 0.05$) and, in cases where small values made the chi-square P values not accurate, the Fisher's exact test ($p < 0.05$) was used. Some proportions also had confidence intervals of 95% determined. Other data were obtained only for the fatal cases whose diagnosis was first obtained at autopsy.

RESULTS

As shown in Table 1, IE clinical data of Group 1 cases showed some differences compared to those of Group 2. IE predisposing diseases,

medical procedures, and infections observed in the fatal cases whose diagnosis was first obtained at autopsy are shown in Table 2.

DISCUSSION

The 31 fatal cases whose diagnosis was first obtained at autopsy strongly influenced the mortality in our IE patients representing 42.4% of all deaths. The IE mortality without this group of patients would decrease from 40.5% to 28.1%. Our results are similar to those reported in other studies analyzing IE in aged higher than 60 years patients with major underlying diseases, showing a 57% mortality compared to 28% of other IE patients³.

The analysis of the clinical data of the 31 IE fatal cases whose diagnosis was first obtained at autopsy (Group 1) showed some significant differences compared to the other 149 IE cases (Group 2), as shown in Table 1. The

average age of 53 years (SD 22.96 years and median of 56 years) in Group 1 patients was 18 years higher than that of Group 2, 35 years (SD 19.1 years and median of 31 years). Both patient groups presented a high frequency of fever. There was a significant difference on frequencies of cardiac murmur ($p < 0.0001$) between the two studied groups. The patients of Group 1 had a lower frequency (25.8%) of cardiac murmur. There was also a significant difference on frequencies of IE predisposing heart disease ($p < 0.0001$). The Group 1 patients showed a lower frequency (25.8%) of IE predisposing heart disease. A lower number of echocardiography tests were performed in Group 1 patients (16.1%, $p < 0.0001$) suggesting that IE diagnosis was not suspected in these cases. Likewise, although most Group 1 patients appeared with severe acute illness, it was reduced the frequency of IE classic clinical signs and symptoms such as splinter hemorrhages and petechiae ($p < 0.0001$), hepatomegaly ($p = 0.001$) and splenomegaly ($p = 0.0298$). Probably, the infection in Group 1 patients was so acute and severe that more than 75% of the cases did not have

Table I

Clinical data of IE cases whose diagnosis was first obtained at autopsy (Group 1) and data collected of the other 149 IE cases (Group 2)

IE cases	Group 1	Group 2
Number of cases	31	149
Male/female ratio	1.38 / 1	2.4 / 1
Average age (SD) and median age in years	53 (22.96), 56	35 (19.1), 31
Predisposing heart disease*	1 (3.2%)	62 (41.6%)
HIV infected patients	0 (0%)	30 (20.1%)
Presence of fever	27 (87%)	130 (87.2%)
Presence of cardiac murmur**	8 (25.8%)	124 (83.2%)
Echocardiography***	5/31 (16.1%)	127/149(85.2%)
Echo evidence of vegetation****	1/5 (20%)	110/127(86.6%)
Endocarditis location (based on necropsy observation for Group 1 patients)	Mitral valve-10 (32.2%) Aortic valve-5 (16.1%) Mitral + aortic-5 (16.1%) Tricuspid – 2 (6.4%) Tric. + mitral– 2 (6.4%) Mitral.+ mural-2 (6.4%) Other – 4 (12.8%)	Mitral valve-50 (33.5%) Tricuspid – 29 (19.4%) Aortic valve-25 (16.7%) Mitral + aortic-5 (3.3%) Pulmonar valve-5(3.3%) Aortic+tricuspid-5 (3.3%) Pulmon. Artery-5(3.3%)
Patient looking severe acutely ill*****	21 (67.7%)	10 (6.7%)
Patient not looking severe acutely ill	10 (32.2%)	139 (93.2%)
Splinter hemorrhages and petechiae *****	8 (25.8%)	124 (83.2)
Hepatomegaly @	4 (12.9%)	67 (44.9%)
Splenomegaly @@	4 (12.9%)	50 (33.5%)
Hemoglobin level < 10 g /dl	14 (45.1%)	72 (48.3%)
Leukocyte count > 11000 / mm ³	21 (67.7%)	64 (42.9%)
Blood culture #	20/31 (64.5%)	148/149 (99.3%)
Isolated microorganism	14/20 (70%)	88/148 (59.4%)*
<i>Staphylococcus aureus</i>	10 (71.4%)	36 (40.9%)
<i>Streptococcus viridans</i>	2 (14.2%)	25 (28.4%)
Other microorganism	2 (14.2%)	32 (36.3%)
Endocarditis-related complications **.##	26 (83.8%)	90 (60.4%)
Cardiac failure	4 (12.9%)	27 (18.1%)
Embolization	16 (51.6%)	50 (33.5%)
Sepsis###	15 (48.3%)	18 (12.0%)
Shock####	9 (29%)	11 (0.6%)
Other causes	4 (12.9%)	Unknown
Deaths (mortality)	31 (100%)	42 (28.1%)

*More than one bacteria isolated in a few blood cultures; ** Several cases had more than one endocarditis-related mortality cause; * $p < 0.0001$; ** $p < 0.0001$; *** $p < 0.0001$; **** $p = 0.0022$; ***** $p < 0.0001$; *****; $p < 0.0001$; @ $p = 0.001$; @@ $p = 0.0298$; # $p < 0.0001$; ## $p = 0.0134$; ### $p < 0.0001$; #### $p = 0.0024$.

Table 2

Infections, predisposing medical procedures, and concomitant diseases observed in the 31 IE cases whose diagnosis was first obtained at autopsy

Infection diagnosed as the causative of fever	Pneumonia-7 (22.5%)
	Urinary infection-3 (9.6%)
	Bacterial meningitis-3 (9.6%)
	Infected eschar 1 (3.2%)
	Septic arthritis 1 (3.2%)
	Infected leg stump 1 (3.2%)
	Lung abscess 1 (3.2%)
	Other 2 (6.4 %)
Predisposing medical procedures	Central intravenous catheters-22 (70.9%)
	Vesical cannula-20 (64.5%)
	Orotracheal cannula-11 (35.4%)
	Recent surgery-10 (32.2%)
	Gastric cannula-9 (29%)
	Other-13 (41.9%)
Concomitant diseases	Malignancy-5 (16.1%)
	Alcohol abuser-3 (9.6%)
	Diabetes – 3 (9.6%)
	Cerebral ischemia-3 (9.6%)

enough time for reticulum-endothelial cells hypertrophy leading to hepatomegaly and splenomegaly. A significantly reduced number of blood cultures ($p < 0.0001$) were performed in the Group 1 patients (64.5%) compared to Group 2 patients (99.3%). Probably, the Group 1 patients had a significantly reduced number of blood cultures performed because some of them had pneumonia, urinary or other infections already diagnosed. However, bacteria were isolated in the blood cultures of 20 patients and *Staphylococcus aureus* was isolated in 10 of these samples. The bacteria attacked mitral and aortic valves that could be normal based on the absence of cardiac murmur.

A higher proportion of infections by *Staphylococcus aureus*, 71.4%, was observed in Group 1 patients and 95% confidence intervals of 0.55 to 0.87, did not superpose to that of Group 2 patients which was of 0.33 to 0.48 (Table 1). This data show that infections by this bacteria were more common in Group 1. Patients of Group 1 also presented a different *Staphylococcus aureus* IE form compared to the better prognostic form which occurs in young patients, have mostly affected the tricuspid valve and the bacteria is acquired by injecting drugs intravenously¹⁰. Studies on *Staphylococcus aureus* IE patients have shown a high mortality risk related to the aged higher than 60 years². A report on a group of patients that did not have clinically suspected IE, showed that 54% of the patients had hospital-acquired infections, 55% presented no heart murmurs initially, and mitral valve was involved in 68%⁵.

In our study, most of the fatal cases whose diagnosis was first obtained at autopsy presented infections located in lungs, urinary tract, and central nervous system (Table 2). These infections were found as an explanation to the fever in 60.9% of the patients. It could be a primary focus of bacterial infection that evolved to IE or it could be a metastasis consequent to the IE bacteremia. The bacterial blood invasion was probably enhanced by medical procedures that were performed in practically all the patients, such as central intravenous catheterization, vesical cannulation, oro-tracheal cannulation or surgery. The patients, besides elderly, 40% had

immunodepressive diseases and/or IE predisposing factors such as tumors and diabetes, besides, 9.6% of the patients were alcohol abusers. Cerebral ischemia observed in about 9.6% could be associated to unsuspected embolizations associated to the IE. In a 1986 study, a high mortality group of *Staphylococcus aureus* IE patients showed many of the characteristics observed in our patients: older than 50 years (average age of 68 years), 32% did not presented cardiac murmur, for 55% of the cases the diagnosis was first obtained at autopsy, and deaths were associated to hospital infections, cardiac failure and embolism².

In our study, a high number of the fatal IE patients (83.8%) presented severe complications such as embolization and cardiac failure. Sepsis occurred in about half of the patients and it was followed by shock in more than ¼ of the patients (Table 1). These severe complications were a leading cause of death as observed by other authors. In a study where IE by *Staphylococcus aureus* struck aortic and mitral valve, most of patients presented cardiac failure and embolism, leading a 71% mortality³. Other studies with *Staphylococcus aureus* IE patients have shown a high mortality risk related to the aged higher than 60 years, longer than 30 days hospitalization, alcoholism and presence of neurological disorders⁵. Likewise, comparing our data with those reported by TIOSSI *et al.*, 1994¹¹, in a study done in São Paulo City, Brazil, their patients with diagnosis done after autopsy also had acute IE occurring mostly after 50 years of age. As in our study, the IE stroked mostly previously normal mitral and aortic valves. It was observed a high frequency of embolization in these IE patients as in our study. The absence of cardiac murmur was more frequent in our patients (74.2%) than in those of that study (46%).

This work was not originally planned as a prospective clinical study. It was motivated by a casual finding during a review of IE cases and the authors realize that the comparison of the 2 patient groups is subject to bias. However, the authors' objective is simply raise awareness for the fact that there is a group of patients, representing 17.2% of the IE cases seen in a general hospital in Ribeirão Preto, SP, Brazil, with unsuspected severe and fatal acute form of IE. The patients are mostly older than 50 years (average age of 53 years, SD 22.96 years and median of 56 years), usually suffer medical procedures that could enhance bacterial spread, and have immunosuppressive diseases such as malignancy and diabetes. The IE in these patients is mostly caused by *Staphylococcus aureus* striking left heart valves, produces massive and virulent bacteremias, endocarditis-related complications such as embolizations and leads to sepsis in almost half of the cases. IE diagnosis is commonly not suspected or have a delayed diagnosis in these cases mostly because of the absence of cardiac murmurs, and the presence of local infections that could explain the fever and other signals. This form of IE must be suspected in mature and in old febrile hospitalized patients having infection predisposing diseases, embolization, and suffering medical procedures. It is important to study and to acquire experience on this IE presentation in order to indicate suitable antimicrobial and surgical treatments, thus reducing the disease mortality.

RESUMO

Endocardite infecciosa (EI) com diagnóstico feito apenas à necrópsia: análise de 31 casos ocorridos entre 1992 e 1997, em Ribeirão Preto, Brasil

Trinta e um casos fatais de EI, que tiveram este diagnóstico apenas à necrópsia, foram analisados. Os dados clínicos destes pacientes (Grupo

1) mostrou diferenças significantes quando comparados aos de outros 141 casos de EI (Grupo 2). A idade média de 53 anos nos pacientes do Grupo 1 foi 18 anos mais alta que nos do Grupo 2. Os pacientes do Grupo 1 tiveram uma baixa frequência de cardiopatias predisponentes à EI. Ambos os grupos de pacientes apresentaram febre (aproximadamente 87%), mas uma significativa baixa frequência de sopro cardíaco (25,8%) foi observado no Grupo 1, provavelmente, em consequência disto, o ecocardiograma foi efetuado em apenas 16,1% dos casos, não sendo, portanto, suspeitada EI. Os pacientes do Grupo 1, embora tivessem grave enfermidade aguda, não apresentaram apresentação clínica compatível com EI clássica. Hemoculturas foram feitas em apenas 64,5% dos pacientes do Grupo 1, porém, isolou-se bactérias em 70% e dentre os isolados, predominou o *Staphylococcus aureus* (71,4%). Foram predominantemente acometidas as válvulas mitral e aórtica. Complicações como embolização e insuficiência cardíaca ocorreram em quase metade dos casos e eles também apresentaram infecções pulmonares, urinárias e do sistema nervoso central. Praticamente todos os casos fatais de EI, que tiveram este diagnóstico apenas à necropsia, foram submetidos a procedimentos médicos. Sepsis aconteceu em aproximadamente metade dos pacientes e mostrou-se acompanhada de choque em mais de 25%. Esta forma de EI deve ser suspeitada em pacientes de idade madura ou idosos, hospitalizados, com doenças que predisõem a infecções, com embolização e que sofreram procedimentos médicos.

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