
A five-year retrospective hospital-based study of endogenous endophthalmitis in south Malaysia

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Abstract

Purpose: To analyse the predisposing factors, microbial profiles, source of infection, and visual outcomes of endogenous endophthalmitis seen in Hospital Sultanah Aminah Johor Bahru (Johor, Malaysia).

Study design: Retrospective review.

Methods: The medical records of 15 patients, of which 19 eyes were diagnosed with endogenous endophthalmitis, admitted from January 2014 to December 2018 were retrospectively reviewed.

Results: The mean age was 55.9 ± 12.7 years (range: 31-78 years of age). There were four patients (26.7%) with bilateral involvement. Diabetes mellitus was the commonest risk factor in this study (odds ratio: 16; 95% confidence interval: 1.09-234.26). The most common source of infection was urosepsis ($n = 3$, 20%) followed by liver abscesses ($n = 2$, 13.3%), *Klebsiella pneumoniae* being the most common microorganism isolated ($n = 4$, 44.4%). Only 10.5% of eyes ($n = 2$) had a final Snellen visual acuity better than 6/60, while 47.4% of eyes ($n = 9$) had vision of no light perception.

Conclusion: In this study, *Klebsiella pneumoniae* was the most common organism. Overall, endogenous endophthalmitis is associated with poor visual outcomes.

Keywords: diabetes mellitus, endogenous endophthalmitis, *Klebsiella pneumoniae*, vitrectomy

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Kajian retrospektif berasaskan hospital selama lima tahun terhadap endoftalmitis endogenus di selatan Semenanjung Malaysia

Abstrak

Tujuan: Untuk menganalisa faktor risiko, profil mikrob, sumber jangkitan, dan kesan penglihatan endoftalmitis endogenus yang dilihat di Hospital Sultanah Aminah Johor Bahru (Johor, Malaysia).

Reka bentuk kajian: Kajian retrospektif.

Kaedah: Rekod perubatan dari 15 pesakit, yang mana 19 mata didiagnosa sebagai endoftalmitis endogenus dari Januari 2014 hingga Disember 2018 telah dikaji secara retrospektif.

Keputusan: Purata umur adalah 55.9 ± 12.7 tahun (julat: 31-78 tahun). Terdapat empat pesakit (26.7%) dengan penglibatan dua mata. Diabetes mellitus adalah faktor risiko paling kerap dalam kajian ini (nisbah odds: 16; 95% selang keyakinan: 1.09-234.26). Sumber jangkitan yang paling kerap ialah urosepsis ($n = 3$, 20%) diikuti oleh abses hati ($n = 2$, 13.3%). *Klebsiella pneumoniae* menjadi mikroorganisma yang paling kerap ditemui ($n = 4$, 44.4%). Hanya 10.5% ($n = 2$ mata) mempunyai ketajaman visual Snellen terakhir yang lebih baik daripada 6/60, manakala 47.4% ($n = 9$ mata) mengalami kebutaan iaitu kehilangan penglihatan walau kepada cahaya.

Kesimpulan: Dalam kajian ini, *Klebsiella pneumoniae* adalah organisma penyebab yang paling kerap ditemui. Secara keseluruhan, endoftalmitis endogenus dikaitkan dengan penglihatan yang kurang baik.

Kata kunci: diabetes mellitus, endoftalmitis endogenus, *Klebsiella pneumoniae*, vitrektomi

Introduction

Endogenous endophthalmitis (EE) is rare and accounts for 2-8% of all cases of endophthalmitis.^{1,2} It is caused by the hematogenous spread of organisms from a remote infective source to the eyes, resulting in severe visual loss. EE is most often associated with several medical conditions such as diabetes mellitus, renal failure, malignancy, acquired immunodeficiency syndrome, in-dwelling catheters, and intravenous drug abuse.³ The spectrum of the causative agent is broad and includes gram-negative bacteria, gram-positive bacteria, and fungi. However, studies show considerable differences in the frequency of these pathogens in relation to geographical areas.^{4,5} The visual outcomes following EE are typically

poor, particularly when a gram-negative organism is identified as the causative agent.^{3,6} Hospital Sultanah Aminah is a tertiary referral hospital that provides service to the entire Johor state, which is located in southern West Malaysia. We aim to identify the epidemiology of EE in the southern part of Malaysia.

Materials and methods

A retrospective review of all patients diagnosed with EE and managed at Hospital Sultanah Aminah Johor Bahru (HSAJB) from January 2014 to December 2018 was conducted.

Inclusion criteria was patients with clinical diagnosis of EE made by an ophthalmologist. Relevant microbial investigations were taken both from blood and vitreous samples via vitreous tap, before the antibiotic injection. The collected samples were inoculated directly on blood agar, Sabouraud, and chocolate agar. Patients with incomplete laboratory data or lost to follow-up in less than one month were excluded.

Demographic characteristics, microbial profiles, management, and initial and final visual acuity (taken at one-month follow-up) were obtained from the patient's medical records, and data were analysed using the IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Data with numerical variables were described as mean and standard deviation, while categorical data were expressed by frequency (*N*) and percentage.

Results

A retrospective review of medical records of 19 eyes of 15 patients diagnosed with EE, including 11 patients (73.3%) with unilateral involvement and 4 (26.7%) with bilateral involvement was conducted. The demographic profiles of the patients are summarized in Table 1.

The 15 patients included 10 males (66.7%) and 5 females (33.3%). The mean age at presentation was 55.9 ± 12.7 years (range: 31-78 years of age). The laterality of the right eye (57.9%) was more common than the left eye (42.1%).

Ten patients had diabetes mellitus (66.7%). Eleven patients (73.3%) had an identifiable source of infection, with urosepsis being the most common ($n = 3$, 20%). Other sources of infection included liver abscesses ($n = 2$, 13%) and pneumonia, neck carbuncle, infected femur implant, scrotal abscess, gingivitis, and infective endocarditis identified in one patient each (6.7%). However, sources of infection could not be identified in three patients (20%). The microorganism was successfully isolated from blood or vitreous samples in nine patients (11 eyes, 60%) with 6 (66.6%) yielding gram-negative organisms, 2 (22.2%) gram-positive organisms, and 1 (11.1%) fungal organisms (Table 2).

Table 1. Clinical characteristics of patients (N = 15)

Patient	Gender	Age	Eye	Medical comorbidities	Systemic infection	Isolate	Vitrectomy	Initial VA	Final VA
1	M	48	RE	DM, HPT, ESRF	Unknown	Gram -ve bacteria	No	CF	NPL
2	M	48	RE	DM	Scrotal abscess	Gram -ve bacteria	No	CF	NPL
3	M	52	RE	DM	Neck carbuncle	Gram -ve bacteria	No	HM	Evisceration
4	F	65	BE	NIL	Infective endocarditis	Gram +ve bacteria	Yes	RE: CF LE: CF	RE: 2/60 LE: 6/36
5	F	78	RE	DM, HPT	Urosepsis	Gram +ve bacteria		HM	HM
6	F	40	RE	DM	Urosepsis	Gram -ve bacteria	No	6/36	6/6
7	M	53	BE	DM, HPT	Cholecystitis	Gram -ve bacteria	No	RE: HM LE: 6/6	RE: NPL LE: HM
8	M	68	RE	DM, HPT	Pneumonia	Gram -ve bacteria	Yes	HM	PL
9	F	64	LE	DM, HPT, dyslipidemia	Unknown	Fungal	No	PL	NPL
10	F	73	LE	DM, HPT, IHD, ESRF	Unknown	No growth	No	NPL	NPL
11	M	46	RE	NIL	Unknown	No growth	No	HM	NPL
12	M	63	LE	HPT	Urosepsis, pneumonia	No growth	Yes	HM	PL
13	M	53	BE	NIL	Gingivitis	No growth	Yes	RE: PL LE: HM	RE: CF LE: 6/60
14	M	57	BE	DM, HPT	Liver abscess	No growth	Yes	RE :HM LE : PL	RE : CF LE : NPL
15	M	31	LE	NIL	Infected femur implant	No growth	No	HM	Evisceration

F: female; M: male; LE: left eye; RE: right eye; BE: both eyes; DM: diabetes mellitus; HPT: hypertension; IHD: ischemic heart disease; ESRF: end-stage renal failure; NPL: non-perceptive to light; PL: perceptive to light; HM: hand movement; CF: counting fingers; VA: visual acuity; Gram -ve, gram-negative; Gram +ve: gram-positive

At presentation, 17 out of 19 eyes had visual acuity worse than 6/60. Four eyes (21%) were counting fingers, 9 eyes (47.4%) could perceive hand movement, 3 (15.8%) were perceptive to light, and 1 eye (5.3%) was no light perception. Two eyes had a relatively good vision of 6/36 and 6/6.

Final visual acuity at least at one-month follow-up showed improvement in 6 eyes (26.3%). One eye (5.3%) showed no improvement and 12 eyes (52.6%) worsened. Eight eyes (42.1%) underwent vitrectomy.

Discussion

EE is a vision-threatening disease that occurs mainly in older patients with underlying debilitating systemic disease. The mean age of presentation in our study was 55.9 ± 12.7 years. This finding is consistent with the study by Jackson *et al.*, which reported that the incidence peaks at about 50 years of age.³ The increased risk with age might be explained by reduced natural immunity in this advanced age group; however, the increased risk with age was only true for very advanced ages (≥ 90 years). The right eye in our study was affected twice as much as the left eye (46.7 vs 26.7), probably due to more proximal and direct arterial blood flow to the right carotid artery.⁷ Studies done by Jackson *et al.* and Leibovitch *et al.*, however, found the carotid artery anatomy has a lesser effect on the spread of EE.^{3,8} A case series by Leibovitch *et al.* observed a male preponderance, similar to our study.⁸

A case series by Jackson *et al.* found that 56% of the patients had an underlying medical condition that predisposed to infection, the commonest being diabetes mellitus.³ Binder *et al.* reported all of their patients had at least one underlying chronic disease, including diabetes mellitus, prosthetic cardiac valves, cancer, chronic obstructive pulmonary disease, permanent pacemaker, rheumatoid arthritis, and end-stage renal failure.⁹

Although our study suggests that gram-negative organisms were the commonest cause of EE, there was considerable variation based on geographical location. In the case series published by Wong *et al.*, the incidence of EE in the Western hospital was caused mostly by gram-positive organisms, while the East Asian hospital was burdened by gram-negative organisms, particularly *Klebsiella* sp.⁵ These findings are consistent with reports from Singapore and Taiwan, which reported 70% of the cases of EE were caused by gram-negative (approximate 60% were *Klebsiella pneumoniae*) organisms, with liver abscess being the major source of infection.^{5,10}

In our study, urosepsis was the common source of infection. We postulate that this is partly due to the fact that our centre is among the only 13 government centres which provide specialized urology services for the whole of Malaysia.¹¹ With a population of 3.31 million, most Johoreans with urosepsis have a higher probability of being treated in our centre, thus contributing to the higher cases of EE secondary to urosepsis.¹² Although our study was conducted on a small sample

Table 2. Microbial isolates from vitreous samples (N = 15)

Organism	N (%)
Culture positive	9 (60)
Gram-positive organisms	2 (22.2)
Streptococcus pneumoniae	1
Group B streptococcus	1
Gram-negative organisms	6 (66.7)
Pseudomonas aeruginosa	1
Klebsiella pneumoniae	4
Escherichia coli	1
Fungal	1 (11.1)
Penicillium sp.	1
Culture negative	6 (40)

Table 3. Reported prevalence of EE in Asian and non-Asian countries

Study		Date range and location	Number of EE cases	Commonest medical comorbidities (%)	Commonest organisms (%)
Asian studies	Wong <i>et al.</i> ⁵	1994 to 1997; Singapore	32	DM (40.7)	<i>K. pneumoniae</i> (60)
	Michael <i>et al.</i> ¹⁹	2012 to 2016; Malaysia	18	DM (88.2)	<i>K. Pneumoniae</i> , <i>P. aeruginosa</i> (17.6)
	Lee <i>et al.</i> ⁶	1996 to 2010; South Korea	97	DM (42.5)	<i>K. pneumoniae</i> (48.4)
Non-Asian studies	Jackson <i>et al.</i> ³	1984 to 2001; England	21	DM (42.1)	<i>E. coli</i> (21.1)
	Okada <i>et al.</i> ⁴	1980 to 2990; USA	32	DM (39.3)	<i>Staphylococcus aureus</i> (25)
	Binder <i>et al.</i> ⁹	1982 to 2000; USA	34	DM and cancer (33)	<i>Candida albicans</i> (37)

DM: diabetes mellitus

population, it did show epidemiologic trends comparable to other studies (Table 3).

Visual outcomes in EE have always been poor, especially in bacterial EE, with gram-negative isolates having a poorer prognosis than gram-positive isolates.^{3,6} This is consistent with other studies reporting poor visual outcomes for patients with bacterial EE. In a systemic review by Schiedler *et al.*, 50% of patients had visual acuity worse than 6/60, while Okada *et al.* reported 78% of patients had visual acuity worse than 6/60.^{4,13}

Poor prognosis in cases of gram-negative organisms is due to an array of virulence factors that enable the bacteria to escape host immune systems and replicate in distant organs. The capsule of gram-negative organisms is known to avert fulminant activation of the immune response by decreasing reactive oxygen species. Ryuzo *et al.* found C reactive protein and interleukin-6 blood levels were significantly higher in gram-negative bacteremia than in gram-positive bacteremia.^{14,15}

The ability of the siderophore to acquire iron in the iron-poor environment during the infection also allows *K. pneumoniae* to colonize and disseminate inside the vitreous cavity.¹⁵

In our study, one of the patients with Klebsiella-associated EE (Table 1, number 7) had a final visual acuity of hand movement despite presenting early with visual acuity of 6/6, showing the virulence of *Klebsiella* sp., which is rapidly destructive despite early treatment.⁴ In most of our patients, the initial systemic antibiotics were selected by the infectious disease physician and were aimed at the source of infection and presumed causative organisms. However, in this particular case, it was initially diagnosed by an ophthalmologist and the initial treatment was ceftazidime and vancomycin according to the European Vitrectomy Study (EVS) protocol. This is likely inappropriate for patients with EE, as the protocol was designed for postoperative endophthalmitis.¹⁶

Because the causative organisms differ in this condition, systemic antibiotics should be selected differently. We suggest that initial empirical antibiotics for patients suspected of having EE should include ceftriaxone to cover *K. pneumoniae* and vancomycin to cover gram-positive organisms.

This, however, differs from one of the patients shown in Table 1 (number 6), who attained functional visual acuity of 6/6 from initial visual acuity 6/36. This patient was given intravitreal antibiotics immediately on the same day of blurred vision in the right eye after being referred from the urology department. In our cases, we postulate that a good initial visual acuity is associated with good final visual acuity, in line with case series from Nishida *et al.* and Binder *et al.*, which described that a good presenting visual acuity was significantly associated with good final visual acuity.^{9,17}

Moreover, Chang *et al.* found that patients with Klebsiella-related liver abscesses have a 3% risk of developing EE.¹⁸ Hence, the physician should be made aware of EE and educate patients about EE, including its symptoms, especially those with Kleb-

siella-related liver abscesses. This in turn will aid ophthalmologists to diagnose and treat EE early.

The data found in this study provided an overview of the varied causative organisms and sources of infection involved in EE. In addition, diabetes mellitus was one of the main risk factors for EE. This indicates that diabetic control must be addressed at multiple levels in the health care system, including improved detection, adherence to the treatment, and systemic health care monitoring and program evaluation.

Conclusion

EE is a rare but often devastating ocular and systemic disorder. It carries a poor prognosis in most patients, especially where gram-negative organisms are involved. Diabetes mellitus remains one of the major risk factors for EE.

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