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Original Article

Isolates and antibiotic susceptibilities of endogenous bacterial endophthalmitis: A retrospective multicenter study in Japan☆

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ABSTRACT

Endogenous bacterial endophthalmitis, also called metastatic endophthalmitis, is a rare bacterial endophthalmitis derived from distant infectious foci via the bloodstream. This infection can potentially cause not only severe visual disturbance, but also loss of the eyeball or death, as most patients are immunocompromised. This retrospective Japanese multicenter study analyzed 32 eyes in 25 definitive cases. Twelve patients (48.0%) had diabetes mellitus. Typical ocular findings were vitreous haze (87.5%), cells in the anterior chambers (62.5%) and retinal infiltrates (50.0%). Elevated body temperature (64.0%), high serum C-reactive protein (96.0%) and leukocytosis (52.0%) were also frequently observed. Culture positivity rates for intraocular fluid were higher in the vitreous (62.5%) versus aqueous humor (28.6%). High positivity rates were also observed for blood (57.1%) and central venous catheters (100%). The most common pathogen was *Staphylococcus aureus* (10 cases), including methicillin-resistant *S. aureus* (4 cases). The next most common pathogen was *Klebsiella pneumoniae* (7 cases), which was highly associated with liver abscess. Compared to a previous 1991 national multicenter study, there has been a fourfold increase in the ratio of *S. aureus*. Antibiotic susceptibility tests revealed that all Gram-positives were susceptible to vancomycin and all Gram-negatives were susceptible to third-generation cephalosporins, imipenem/cilastatin, gentamycin and levofloxacin. Prognostic factors influencing poor visual outcome included poor initial visual acuity ($p < 0.01$), *K. pneumoniae* ($p = 0.027$) and gram-negative bacteria ($p = 0.014$) as the causative bacteria. Intravitreal antibiotic injection in combination with vancomycin and ceftazidime may be applicable for use as part of the standard treatment regimen for EBE.

1. Introduction

Bacterial endophthalmitis is a rapidly progressive intraocular infection that often devastates retinal function and causes blindness. Bacterial endophthalmitis includes postoperative, post-traumatic, and endogenous endophthalmitis. Since there are no remarkable episodes such as prior ocular surgeries or trauma associated with endogenous endophthalmitis, this infection is the most difficult to diagnose. Furthermore, in order to ensure correct referrals to appropriate clinical departments, ophthalmologists also need to determine the patients' backgrounds and co-morbidities. Due to the recent publication of guidelines for endogenous fungal

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endophthalmitis, this has led to a better understanding of the diagnosis, management and treatment of the infection [1]. However, there have yet to be any guidelines published for endogenous bacterial endophthalmitis (EBE). Indeed, it has been reported that 24–33% of all EBE cases were misdiagnosed as other ophthalmologic conditions, including diagnoses of non-infectious uveitis, fungal endophthalmitis, acute angle closure glaucoma and conjunctivitis [2]. Delays due to misdiagnoses not only can lead to a poor visual prognosis, but also death due the worsening of the systemic infection. Thus, it is important to update and report on the definitive clinical characteristics of ocular, physical, serological and microbiological examinations to ensure that a prompt diagnosis is made. Recently, there has been an increased isolation rate of extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* [3]. The most common causative organism of EBE in the Asian population is *Klebsiella pneumoniae* [4–8]. Thus, the antibiotic susceptibilities of isolates need to be periodically updated in order to ensure that clinicians can determine whether the intravitreal injections that are widely used as first-line drugs for EBE [2], such as the combination of vancomycin (VCM) and ceftazidime (CAZ), are still appropriate. However, with the exception of a recent single-center study [9], there has not been a large national surveillance study reported in Japan since 1991 [10]. In our current study, we performed a retrospective multicenter study and investigated the clinical characteristics, causative bacteria, sources of infection, antibiotic susceptibilities, culture positive rates of various clinical samples, and the prognostic factors that lead to a poor visual outcome.

2. Patients and methods

We conducted this multicenter retrospective study in order to identify clinical findings, source of infection, causative bacteria, antibiotic susceptibilities, culture positive rates of various bacterial samples, and prognostic factors leading to poor visual outcome. The participating tertiary hospitals were as follows: Gunma University Hospital, Gifu University Hospital, Tokushima University Hospital, Tokyo Medical University Hospital, Ehime University Hospital, and Miyata Eye Hospital. This study was approved by the Ethics Committees of the respective hospitals. From 2009 to 2014, this study examined 32 eyes in 25 patients who were diagnosed as EBE with positive bacterial cultures for samples from the aqueous humor, vitreous, blood or central venous catheter. Medical records were reviewed at the initial visits. Items examined included: age, sex, affected eye (right, left or both), co-morbidities, sources of infection, best-corrected visual acuities (BCVA), intraocular pressures, findings in slit lamp examinations, indirect fundus examinations, B-mode ultrasonography (when fundus was invisible), and body temperature. Serological tests were also performed to evaluate C-reactive proteins (CRP), white blood cell counts, platelet counts, fibrin/fibrinogen degradation products (FDP), D-dimer and beta-D-glucan. Bacterial isolates from cultures of the aqueous humor or vitreous were considered as the causative bacteria, while isolates from the cultures of blood or the CV catheter were considered as the presumed causative bacteria. Antibiotic susceptibilities of causative or presumed causative bacteria were also reviewed. An antimicrobiotic susceptibility test was performed using the microdilution method at each hospital, with all results interpreted according to the Clinical and Laboratory Standards Institute (CLSI) standard method (M100-S19). A medical records review was performed to determine the medical and surgical treatments including systemic antibiotics, intravitreal antibiotics injections and vitrectomy surgeries. Sources of infection were defined comprehensively from the consistence of the bacterial isolates, the time course from the development of the prior extra-ocular infection, and the exclusion of the other causes of endophthalmitis. The diagnosis of catheter-related bloodstream infection (CRBSI) was performed in accordance with the established guideline [11]. Bacteremia was defined as a positive bacterium by blood culture. Clinical outcomes including final BCVA, phthisis bulbi, evisceration or enucleation and death within 3 months of the initial visits were also reviewed.

Statistical analysis of the factors influencing poor visual outcome was performed using Fisher's exact test with one degree of freedom by Excel 2010 (Microsoft, Redmond, WA) in conjugation with the add-in software Statcel3 (OMS Inc., Tokorozawa, Japan) [12]. *P* values less than 0.05 were deemed to indicate statistical significance. Poor visual outcome was defined as the BCVA at the last visit or at 3 months when the follow-up period was longer than 3 months.

3. Results

3.1. Patient characteristics and co-morbidities

This study included 32 eyes of 25 patients (11 males and 14 females), with ages ranging from 41 to 84 years (the average: 71.4 years). Eyes were affected bilaterally in 7 patients, and unilaterally in 18, with 12 right eyes and 6 left eyes affected. The most frequent co-morbidities included diabetes mellitus in 12 patients (48.0%), malignancies in 5 patients (20.0%), immunosuppressive therapies in 5 patients (20.0%) and post-surgery in 5 patients (20.0%).

3.2. Findings for the ocular, physical and serological examinations

Table 1 lists the ocular, physical and serological clinical examinations performed at the first visits. Approximately 40% of the patients exhibited a poor BCVA that was lower than 0.01. Among the ocular findings, vitreous haze (87.5%) was the most common, followed by cells in the anterior chambers (62.5%) and retinal infiltrates (50.0%). An elevated body temperature was observed during the physical examination in 64.0% of the patients. The serological examinations showed that there was a high serum CRP in most of the EBE patients (96.0%) and leukocytosis (52.0%).

Table 1
Ocular, physical and serological findings at the first visit.

		Number[a] (%)
Ocular findings		
Visual acuities[b]	≥0.2	9 (28.1)
	0.01–0.1	7 (21.9)
	CF, HM, LP or NLP	13 (40.6)
Elevated IOP		3 (9.4)
Cells in the AC		20 (62.5)
Fibrins in the AC		8 (25.0)
Hypopyon		14 (43.8)
Vitreous haze[c]		28 (87.5)
Retinal infiltrates		16 (50.0)
Physical findings		
Elevated body temperature		16 (64.0)
Serological findings		
High serum CRP		24 (96.0)
Leukocytosis		13 (52.0)
Thrombocytopenia		8 (32.0)
Elevated FDP		8 (32.0)
Elevated D-dimer		8 (32.0)
Elevated beta-D-glucan		4 (16.0)

CF, counting fingers; *HM*, hand motion; *LP*, light perception; *NLP*, non-light perception; *IOP*, intraocular pressure; *AC*, anterior chamber; *CRP*, C-reactive protein; *FDP*, fibrin/fibrinogen degradation product.
[a] Total number of eyes and patients are 32 and 25, respectively.
[b] Best-corrected visual acuities (decimal).
[c] Observed by indirect funduscopy or B-mode ultrasonography.

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