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INFLAMMATORY DISORDERS

59 eyes with endogenous endophthalmitis– causes, outcomes and mortality in a Danish population between 2000 and 2016

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Abstract
Background To study the epidemiology of patients with endogenous endophthalmitis in Denmark.
Material and methods Retrospective and prospective case series of 59 eyes in patients with endogenous endophthalmitis in Denmark between 2000 and 2016.
Results The age of the patients ranged from 28 to 90 years with a median of 66 years. Sixty-two percent of the eyes had a final VA (visual acuity) ≤ 0.1 while 8% had a final VA ≥ 1.0. Positive cultures were obtained in 51% of the cases from the blood and in 43% from the vitreous. *Streptococcus* species and *Staphylococcus aureus* were the most commonly identified microorganisms. The sources of endogenous endophthalmitis were diverse and were not identified in 36% of the patients. Diabetes (36%) was the most predisposing medical illness. A total of 15% of the patients died within the first year after surgery for endophthalmitis and half of the patients died during follow up. The mortality of patients was 22.6 times higher compared to a Danish background population. Culture positive patients had a higher mortality compared to culture negative patients.
Conclusions Endogenous endophthalmitis is a heterogeneous condition which is reflected in the age, the visual outcome and the mortality of the patients. The epidemiology of the disease is very different in Scandinavia compared to Asia. The visual prognosis remains grave and the majority of the eyes lose useful vision.

Keywords Endogenous endophthalmitis · Visual outcome · Epidemiology · Mortality

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Introduction

Endogenous endophthalmitis (EE) is a rare and very serious intraocular condition that occurs when microorganisms in the blood enter the eye by crossing the blood-retinal barrier. Most publications on this disease are small case reports or case studies and there are no randomized studies on this subject. EE has been shown to occur in 0.05% - 0.4% of patients with fungemia, in 0.04% of patients with bacteremia [1] and to account for 10–18% of all cases of endophthalmitis [2, 3]. The diagnosis of EE is difficult given its low incidence and it is easily missed or misdiagnosed because it mimics common ophthalmological conditions such as uveitis [4, 5]. The visual prognosis is grave in most cases, although some patients achieve excellent vision ([5–8]).

EE is often related to immunosuppressive conditions such as diabetes and cancer as well as endocarditis, liver abscesses and intravenous drug abuse, but can occur in patients who are immunocompetent [7]. There is broad consensus that intravenous antibiotics are mandatory in the treatment of EE, but the role of intravitreal antibiotics, intravitreal steroids, vitrectomy and vitreous tap is unclear ([5, 7, 9]).

The purpose of this study is to report on the characteristics of EE in patients who were diagnosed with this condition at two hospitals in Denmark over a 16-year period between 2000 and 2016. We present data on the sources, the causative

microorganisms, the visual outcomes and the mortality in these patients.

Material and methods

The study was approved by the Danish Data protection Agency (journal number 2012–41-1285) and by the Danish Board of Health (journal number: H-2-2011-004). Patients with EE were identified both retro- and prospectively. First, data from the Danish National Patient Register (NPR) was used to identify all possible cases of EE in the period January 1st 2000 – March 31st 2013 at two ophthalmology departments (Rigshospitalet Glostrup and Naestved hospital). The details in the NPR search strategy have been described in a previous paper [10]. Secondly, patients were identified prospectively from April 1st 2013 – June 1st 2016 at the same two departments. Data on 9 patients in this paper have been published previously [3]. All patient charts were reviewed to confirm the diagnoses.

EE was defined as a condition in which a patient, who had no history of previous recent ocular surgery or trauma, was suspected of having EE by a vitreoretinal surgeon and had a vitrectomy or a vitreous tap performed with the injection of vancomycin and ceftazidime. However, one patient with a positive blood culture (candidemia) and clinical signs of EE was also included, even though the vitreoretinal surgeon refrained from intraocular surgery due to the severity of the patient's underlying disease.

Visual acuity (VA) outcomes were calculated as LogMAR (Logarithm of the Minimum Angle of Resolution) outcomes and converted to Snellen VA outcomes. A visual acuity of counting fingers, hand movements, light perception and no light perception were assigned LogMAR values of 2, 3, 4 and 5, respectively. The outcome of the microbiological analyses was assessed by chart review. An ocular sample was defined as culture positive if it was culture positive from the vitreous cavity.

An administrative system at Rigshospitalet Glostrup was accessed on September 9, 2016, which was the end of follow up date, to determine if the patients had died, and if so, the date of death. In the calculation of the standard mortality ratio (SMR), patients were followed from the day of surgery for EE until date of death or the end of follow up. Official Danish life tables from the period 2006–2010 were used to compare the mortality in our cohort of patients with the mortality in the Danish background population.

Results

A total of 59 eyes in 50 patients with EE were included, of which 34 patients were male. The age of the patients ranged from 28 to 90 years with a median of 66 years. Eighteen cases had only right eye involvement, 23 cases had only left eye involvement and 9 cases were bilateral. A summary of the sources of EE is shown in Table 1 and the result of the blood and vitreous culture tests are shown in Table 2.

In 36% of the patients, the source of the original infection was not found. A microorganism was found either in the blood or the vitreous in 63% of the patients. In 22% of the patients, the same microorganism was found in the vitreous and in the blood. In 20% of the patients no microorganism could be found either from the blood or from the vitreous. In 3 patients, the blood culture was not taken and in one patient the vitreous culture was not taken. The culture results were equivocal in 8 patients. Diabetes (36%) and cancer (26%) were the most common predisposing medical illnesses, see Table 3. Six patients (12%) had no history of any known medical conditions.

The median presenting visual acuity was LogMAR = 3 while the median final visual acuity was LogMAR = 4. In total, 62% of the eyes ended up with a VA ≤ 0.1, 26% of the eyes achieved a final VA ≥ 0.5 while 8% ended up with VA ≥ 1.0. In all, 42% of the eyes had additional eye surgery. A total of 12% of the eyes were enucleated or eviscerated, 14% had retinal detachment surgery, 15% had the lens removed and 2% had surgery for vitreous opacities.

In all, 15% of the patients died during the first year after surgery for EE and more than half of the deaths occurred within the first 2 years after surgery. Half of the patients died during follow up. Overall, the patients had a SMR of 22.6. Patients who were culture positive had a SMR of 24.1 while patients who were culture-negative had a SMR of 14.8, see Table 4.

Discussion

We present the largest case series on EE in Scandinavia, which is a region where the epidemiology of EE has not been described thoroughly. The most recent case series on EE from Denmark consisted of 4 cases of bilateral EE [11]. There are a

Table 1 Sources of endogenous endophthalmitis

Unknown	36%
Cutaneous ulcer*	18%
Endocarditis	12%
Urosepsis/ haemodialysis	10%
Abdominal infection	6%
Pneumonia	6%
Postsurgical (jaw, intestines)	6%
Intravenous tube	4%
Meningitis	2%

* Ulcer of the foot, arm, groin, sternum or back

Table 2 Results of the blood and vitreous culture

	Blood culture	Vitreous culture
Negative	**34%**	**55%**
Positive	**51%**	**43%**
Streptococcus species	21%	16%
Staphylococcus aureus	13%	8%
Polymicrobial growth*	4%	4%
Klebsiella pneumoniae	4%	2%
Enterococcus faecalis	2%	2%
Candida albicans	2%	10%
Propionibacterium acnes	2%	–
Staphylococcus epidermidis	2%	–

•The blood culture results are based on 47 patients because in 3 patients no blood culture was taken

•The vitreous culture results are based on 49 patients because in one case a vitreous sample was not taken due to the severity of the patient's disease

•In 7 patients (14%) the result of the blood culture was equivocal and in one patient the vitreous culture was equivocal

* The 2 cases with polymicrobial growth from the blood:

1) Klebsiella penumoniae and pseudomonas aeruginosa

2) Enterococcus faecalis and candida albicans

* The 2 cases with polymicrobial growth from the vitreous:

1) candida albicans and *Staphylococcus albus* staphylococcus haemolyticus and streptococcus species

few other and larger case series in the literature, but these are primarily from Asia, the U.S. or Australia [9]. The visual morbidity is grave in these patients and 62% of the eyes in this study obtained a final VA ≤ 0.1, while 12% of the eyes were removed. However, the study also shows the EE is a heterogeneous condition, since 26% of the patients ended up with a final VA ≥ 0.5 while 8% obtained a VA ≥ 1.0.

This is the first study on EE that assesses the mortality in patients with EE compared to a background population. The mortality in these patients was high and culture positive patients had a higher mortality compared to patients who were culture negative. In all, 15% of the patients died within the first year after surgery for EE and half of the patients died during follow up. In patients with candidemia who have eye involvement the median survival time has been shown to be 77 days [12]. We believe that this might explain why the mortality was not higher in our cohort because we only identified two patients with a fungal infection (both *Candida* species) in the blood.

Table 3 Known medical illnesses in patients with endogenous endophthalmitis

	No.
Diabetes	36%
Cancer or a history of cancer	26%
Other chronic medical conditions*	24%
Heart disease	16%
Intravenous drug abuse	8%
No history of medical illness	12%

*Chronic obstructive pulmonary disease, tuberculosis, psoriasis arthritis, liver cirrhosis, inflammatory bowel disease, hepatitis C, gout, takayasu arteritis

Table 4 Standardized mortality ratio (SMR) in patients with EE

	SMR	SMR (95% CI)
Culture negative patients	14.8	3.7–59.3
Culture positive patients*	24.1	15–38.8
All patients	**22.6**	**14.4–35.5**

*culture positive blood samples and/or vitreous samples

A microorganism was found either in the blood or the vitreous in 63% of the patients. In 22% of the patients, the same microorganism was found in the vitreous and in the blood. In 20% of the cases no microorganism was found and in the remaining patients the culture results were equivocal. *Streptococcus* species and *Staphylococcus aureus* were the most commonly identified bacteria. This is consistent with other reports where gram-positive bacteria have been shown to be the most commonly identified microorganisms in EE patients in the Western world [13–15]. These species were found in roughly 1/3 of the patients' blood and in ¼ of the patients' vitreous. In contrast, gram negative bacteria have been shown to be predominant in Asian EE patients [7, 16].

There was not a single major source of EE in these patients. A total of 18% of the patients developed EE due to a cutaneous ulcer, while endocarditis was responsible for 12% of the cases. In East Asia, hepatobiliary tract infections with *Klebisiella* species have been shown to account for almost half of the sources of sepsis that lead to EE [7]. *Klebsiella* liver abscesses is a very rare condition in the Danish population and *Klebsiella pneumoniae* was found in only one patient in this study. This shows that there is considerable regional variation when it comes to the underlying microorganisms that cause EE.

Positive cultures were obtained in 43% of the cases from the vitreous and in 51% from the blood. These findings are somewhat similar to the major review by Jackson et al. [5], who found a positive vitreous culture in 40% and a positive blood culture in 60% of the cases. However, Connell et al. have shown a much higher percentage of culture-positive cases in an Australian setting [9]. This shows that it is very important to obtain a blood culture before commencing intravenous treatment in these patients, because it is the most reliable way to establish the diagnosis. In 3 patients the blood cultures were not taken for unknown reasons. These cases occurred between 2000 and 2003 and we believe that this is a clinical mistake that does not occur anymore.

Fungal infections were only found in the blood in 2 patients but in the vitreous of 6 patients (*candida* species). Candidemia is intermittent and may not have been there when the blood cultures were taken. Also, fungal sepsis may not have been considered when the blood cultures were taken, so that the relevant media were not used. In contrast to our findings, Ness et al. [13] studied 31 eyes with EE in Germany and found that *Candida* species were the causative microorganism in 52% of the cases. This is in line with the findings by Connell et al. in Australia [9] who found fungal isolates in 66% of the patients and Schiedler et al. in the U.S. [8] who found fungal isolates in 62% of the patients. A likely explanation for our low number of fungal infections is that we did not include the worst cases of EE, because the patients were too sick to have surgery and therefore were not identified retrospectively. Another explanation is that intravenous drug abuse, which is a well-known risk factor for fungal sepsis, was found in only a minority of the patients.

EE is a disorder that can affect all age groups [5, 7, 13] and can occur uni- or bilaterally. We noted a male predominance (68%), which is a finding that is consistent with the literature [7, 15]. The reason for this finding is unknown. Bilateral involvement was found in 18% of the patients, which is also similar to other studies [7].

We found that 88% of the patients had an underlying illness while 12% were without any known illnesses. Diabetes is known as the most common predisposing illness in patients with EE [5, 7, 8, 15, 16] and was found in 36% of the patients in this study. We found that 26% of the patients had cancer or a history of cancer and 24% were known to have other chronic medical conditions. Intravenous drug abuse, which is believed to be a major risk factor for developing EE [9, 13, 17, 18], was noted in only 8% of the patients, which is in stark contrast to the findings by Connell et al. in Australia, who found intravenous drug abuse to be the most common risk factor, occurring in 38% of the patients [9].

The limitation of this study is its retrospective design and relatively small sample size, which is the reason we refrained from making major statistical analyses. The study is biased towards including only patients who had surgical intervention for endophthalmitis, so we might have missed cases that did not come to ophthalmological attention.

In conclusion, the epidemiology of EE in patients from Scandinavia differs from patients in Asia. To identify these patients better we need to improve the cooperation between internists and ophthalmologists. Many clinicians might fail to notice the overlap between extraocular and ocular disease, but the internist can play a major part in recognizing that there is an eye problem and referring the patient to an ophthalmologist. In this case series, the source of EE was not found in 36% of the patients. If we can become better at diagnosing these patients by attaining a higher awareness of the disease, it is likely that patients will be diagnosed earlier, which will improve their chance of a better outcome.

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Compliance with Ethical Standards

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Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent: Informed consent was obtained from all individual participants included in the prospective part of this study.

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