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Effects of the COVID-19 pandemic on clinical manifestations and therapeutic outcomes in acute endophthalmitis

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ABSTRACT

Endophthalmitis incidence and clinical characteristics was reported to change during Covid-19 pandemic, due to multiple influencing factors, such as prolonged lockdown periods, persistent immune suppression following Sars-Cov-2 infection, and mask wearing. We conducted a retrospective eight-year study, during January 2016 and December 2023, that aims to investigates the differences in terms of etiology, clinical characteristics and outcomes in cases with acute endophthalmitis, admitted before (2016-2019) and during Covid-19 pandemic (2020-2023). The two study subgroups were homogenous in term of age, gender distribution, associated comorbidities, and addressability. During Covid-19 pandemic there were significant delays in presentation ($p=0.02$), more cases of endogenous endophthalmitis ($p=0.025$), and patients presented a more intense systemic inflammatory reaction ($p<0.01$). Moreover, undiagnosed cases of diabetes were more frequent in pandemic group, and were associated with endogenous endophthalmitis (59.3% vs 16.6%, $p<0.001$). The were differences in etiology between the two subgroups, the first cases of hypervirulent Klebsiella pneumoniae endogenous endophthalmitis reported in our center. The outcomes were comparable in terms of hospital stay and rate of evisceration. However, the visual function was worse in the pandemic group, which may be correlated with the specific differences in etiology and delayed presentation. Early diagnosis and prompt initiation of large spectrum antibiotherapy are essential to preserve vision.

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Introduction

Endophthalmitis is a rare, but devastating ocular condition, that is characterized by infection and colonization with microorganisms of the inner layers of the eyeball [1]. According to the entry site, it may be classified as exogenous, related to severe ocular surface infections, ocular trauma or recent surgery, or endogenous, a blood-borne metastatic infection from a distant site [2,3]. Unless early diagnosed and treated, it leads to severe visual impairment or even blindness [4,5].

Several reports found modified clinic-pathological characteristics in endophthalmitis during COVID-19 pandemic [6-8]. A multicenter study of Fortes et al. [6]

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found poorer outcomes in patients with endophthalmitis during pandemic, that may be partially explained by the delayed presentation associated with repeated lockdowns [8,9].

Moreover, several reports present endogenous endophthalmitis in critically ill Covid-19 patients in intensive care [7,9,10]. Abdelkader et al. [7] found that combined endophthalmitis and orbital cellulitis is a factor of poor visual prognosis in Covid-19 infected patients. Khatwani et al. [8] found an increased incidence of endophthalmitis during COVID-19 pandemic, possibly correlated with prolonged post-Covid immune suppression [8]. Another hypothesis is that high-dose corticosteroid therapy in the management of moderate and severe COVID-19 infection may lead to impaired immunity and endogenous endophthalmitis, either bacterial or fungal [10].

The presents study aims to investigates the differences in terms of etiology, clinical characteristics and outcomes in cases with acute endophthalmitis.

Materials and Methods

Study design

An 8-year retrospective study was carried out in the Ophthalmologic Department of Emergency University Hospital, between January 2016 and December 2023. All patients aged over 18 years, admitted with the diagnostic of acute endophthalmitis were included in the analysis. Demographic characteristics, clinical and paraclinical data, were extracted from patients' electronic records and surgical reports.

All patients were documented for age, sex, associated comorbidities, time elapsed from the onset, clinical exam at admission, imagistic and biological data, pathogen identification, therapy and outcomes. The term of acute postoperative endophthalmitis was defined according to the Endophthalmitis Vitrectomy Study (EVS) study as endophthalmitis with early onset, within 6 weeks from the initial surgery [11,12]. Patients with incomplete documentation, those with chronic postoperative endophthalmitis, and those re-admitted for chronic condition associated with a previously diagnosed acute endophthalmitis more than 30 days before were excluded from the analysis.

Based on the date of admission in our department, the study group was divided in a pre-pandemic subgroup (2016-2019) and a Covid-19 pandemic subgroup (2020-2023). The two subgroups were comparatively analyzed in terms of time from the onset, clinical presentation, identification of the pathogen, and therapeutic strategy. The outcomes were studied in terms of final visual acuity in the affected eye, rate of evisceration/enucleation, and the length of hospital stay.

Statistical analysis

Statistical analysis was performed with EasyMedStat (version 3.36; www.easymedstat.com), and Med Calc® Statistical Software (version 22.006 Med Calc Software Ltd., Ostend, Belgium). Continuous variables were expressed as mean (±SD) and discrete parameters as absolute numbers and relative (%) frequencies. Group comparability was assessed by comparing baseline demographic data and follow-up duration between groups. Normality and heteroskedasticity of continuous data were assessed with Shapiro-Wilk and Levene's test respectively. Continuous outcomes were compared with unpaired Student t-test, Welch t-test or Mann-Whitney U test according to data distribution. Correlations were assessed by Pearson's Chi-squared test and Fisher exact test for discrete variables. A p-value of <0.05 was considered statistically significant.

Results

During the 8-years inclusion period, a total number 56 patients were referred to our department for acute endophthalmitis, with a mean age of 65.4±13.2 years. During the COVID-19 pandemic, the number of cases was higher (32 patients, 57.4%) compared to pre-pandemic group (24, 42.3%). There were not significant differences in terms of age, gender, addressability, or associated comorbidities between the 2 study groups. The comparative general data are presented in Table 1.

In our study, we found in a significant delayed presentation in COVID-19 pandemic group compared to pre-pandemic group (mean time: 8.69 vs 3.42 days, p=0.02), which may be correlated with difficulties in accessibility to ophthalmology services due to lock-down periods. Moreover, there were a significant higher rate of endogenous endophthalmitis during COVID-19 period (50% vs 26.3%, p=0.025), with more severe presentation, in terms of fever (p=0.008), associated exophthalmia (p=0.05) and impaired ocular motility (p=0.012).

Diagnosis of acute endophthalmitis was generally based on ophthalmological clinical findings and ocular echography. Clinical presentation showed a decreased visual acuity, varying from counting fingers (CF) to no light perception (no LP), conjunctival hyperemia, variable degrees of corneal edema and turbidity of aqueous humor. Hypopyon (69.6%) and seclusion papillae (67.8%) were considered a factor reflecting the severity of inflammation, and they were encountered with similar rate between the two subgroups (Table 2).

There were significant more cases with systemic inflammatory response and leukocytosis (p=0.03) in the COVID-19 pandemic group. Moreover, a higher rate of raised glycemic values were noticed in the pandemic group, while the differences in previously diagnosed diabetes were not significant between groups, which strongly suggests an associated ignored diabetes or prediabetes in these patients.

Table 1. General data of the patients included in the study group

Parameter	Total group (n=56)	Pre-pandemic group (n=24)	Covid-19 Pandemic group (n=32)	p-value
Age	65.4±13.2	64.17 (± 17.98)	66.38 (± 8.86)	0.87
Gender (male, n; %)	26 (46.4%)	10 (41.6%)	16 (50%)	0.72
Rural area	36 (64.2%)	18 (75.0%)	18 (56.25%)	0.17
Diabetes	8 (14.3%)	2 (8.33%)	6 (18.75%)	0.44
Neoplasm (chemotherapy catheter)	4 (7.1%)	0 (0%)	4 (12.5%)	0.17
Chronic renal disease (with dialysis)	6 (10.7%)	4 (16.67%)	2 (6.25%)	0.32
History of recent ocular surgery (including intravitreal injections)	22 (39.2%)	10 (41.67%)	12 (37.5%)	0.78
History of recent ocular trauma	6 (10.7%)	4 (16.67%)	2 (6.25%)	0.32
Recent history of COVID-19 (<30 days)	2 (3.5%)	0 (0%)	2 (6.25%)	0.28
Time lapsed from onset to presentation	6.43 (±7.76)	3.42 (± 2.41)	8.69 (± 9.6)	0.02*
Location: • Bilateral • Right eye • Left eye	 4 (7.1%) 32 (57.1%) 20 (35.7%)	 0 (0.0%) 14 (58.33%) 10 (41.67%)	 4 (12.5%) 18 (56.25%) 10 (31.25%)	0.19
Cause: • Endogenous • Exogenous	 21 (37.5%) 35 (33.5%)	 5 (26.3%) 19 (73.7%)	 16 (50%) 16 (50%)	0.025*
Associated orbital cellulitis at admission	10 (17.8%)	2 (8.33%)	8 (25.0%)	0.16
Fever (at admission)	11 (19.6%)	1 (4.1%)	10 (33.3%)	0.008*
Exophthalmia	12 (21.4%)	2 (8.33%)	10 (31.25%)	0.05*
Impaired ocular motility	14 (25%)	2 (8.33%)	12 (40.0%)	0.012*

*Footnote: * statistically significant*

Table 2. Clinical and paraclinical findings in patients with endophthalmitis included in the study

Parameter	Total group (n=56)	Pre-pandemic group (n=24)	Covid-19 Pandemic group (n=32)	p-value
BCVA at admission: • CF<1m • HM • LP • No LP	 6 (10.7%) 16 (28.5%) 18 (32.3%) 16 (28.5%)	 2 (8.33%) 8 (33.3%) 8 (33.3%) 6 (25%)	 4 (12.5%) 8 (25%) 10 (31.2%) 10 (31.2%)	0.118
IOP at admission • Normal • Hypertonicity • Hypotonicity	 24 (42.8%) 27 (48.3%) 5 (8.9%)	 10 (41.6%) 11 (45.8%) 3 (12.5%)	 14 (46.67%) 16 (50%) 2 (6.65%)	0.117
Chemosis	20 (35.7%)	6 (25.0%)	14 (43.75%)	0.171
Keratic precipitates	24 (42.8%)	10 (41.67%)	14 (43.75%)	>0.99
Hypopyon	38 (69.6%)	18 (75%)	20 (62.5%)	0.47
Seclusio pupillae	38 (67.8%)	16 (66.6%)	22 (68.5%)	0.32
Ocular fundus • Obscured due to vitritis • Vitreous haze, retinal hemorrhages	 54 (96.4%) 2(3.6%)	 24 (100%)	 30 (93.7%) 2 (6.3%)	0.5
Ocular ultrasound exam (B-mode) • Intense vitreous echogenicity • Retinal detachment • Localized collection	 53 (94.6%) 12 (21.4%) 3 (5.3%)	 23 (95.8%) 4 (16.6%) 1 (4.1%)	 30 (93.7%) 8 (25%) 2 (6.25%)	0.08
Culture for pathogen identification: • Conjunctival swab • Vitreous tap	 36 (64.2%) 14 (25%)	 14 (58.33%) 8 (33.33%)	 22 (68.75%) 6 (18.75%)	0.52

• Hemoculture • Catheter culture • Hepatic abscess • Uroculture	6 (10.7%) 2 (3.57%) 3 (5.35%) 2 (3.57%)	2 (8.33%) 0 0 0	4 (12.5%) 2 (6.25%) 3 (9.3%) 2 (6.25%)	
Pathogen: • Not identified • Cocobacillus • Fungi • Klebsiella pneumoniae • Pseudomonas	40 (71.4%) 2 (3.5%) 4 (7%) 4 (7%) 4 (7%)	16 (66.67%) 2 (8.33%) 4 (16.67%) 0 (0.0%) 2 (8.33%)	24 (80.0%) 0 (0.0%) 1 (3.1%) 4 (13.33%) 2 (6.67%)	0.01*
WBC (cells/mmc; mean±SD)	11.11 (±4.81)	10.66 (± 5.5)	12.15 (± 4.36)	0.138
WBC>10000 cells/mmc (n, %)	25 (44.6%)	7 (29.1%)	18 (56.2%)	0.03*
Fibrinogen (mg/dl; mean±SD)	413.78 (±169.78)	349.42 (± 138.0)	454.0 (± 179.82)	0.01*
Fibrinogen>400 mg/dl (n, %)	20 (35.7%)	4 (16.6%)	16 (50%)	0.009*
CRP (mg/dl; mean±SD)	3.46 ± 4.39)	2.02 (± 1.93)	4.36 (± 5.28)	0.1
CRP>0.5 mg/dl (n, %)	42 (75%)	14 (50%)	28 (87.5%)	<0.001*
Glycemia (mg/dl; mean±SD	119.74 (±34.83)	104.0 (± 26.33)	130.56 (± 36.71)	0.006*
Glycemia >110 mg/dl	23 (41%)	4 (16.6%)	19 (59.3%)	0.001*
CT/IRM for involved orbit	10 (17.8%)	2 (8.33%)	8 (25%)	0.1
Footnote: BCVA: best corrected visual acuity; CF: counting fingers; HM: hand movement; LP: light perception;WBC: white blood cells; CRP: C-reactive protein; * statistically significant (p<0.05)				

Various ultrasound findings have been reported in patients with endophthalmitis included in the study, including heterogeneous debris in the vitreous humor, increased vitreous density. In 3 (5,3%) cases of postoperative endophthalmitis, a limited collection of increased echogenicity was noticed behind the artificial lens. Retinal detachment due to tractional inflammatory membranes was encountered in 24.4% cases, and it was associated with poor visual outcome (Figure 1).

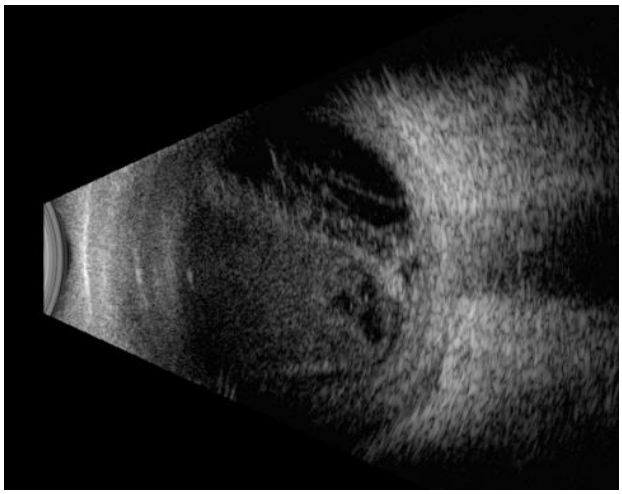

Figure 1. Ultrasound exam showing increased vitreous echogenicity and total retinal detachment

When infection was suspected to extend beyond the ocular globe limits, CT or IRM exam of the orbit was performed, to assess the presence of associated orbital abscess, or orbital cellulitis, perforation of the globe, panophthalmia, of possible intracranial extension of the infection (Figure 2).

In the absence of ocular risk factors for endophthalmitis, a detailed systemic examination was performed in each patient to identify a possible cause of sepsis, including imagistic abdominal and thoracic examination and multiple microbiological culture from potential entry sites (catheter, uroculture, abscess fluid). However, the etiologic agent remained unidentified in 71.6% cases (66.67% vs 80%, respectively), which imposed an empiric large spectrum anti-bacterial and antifungal in both systemic and topic administration.

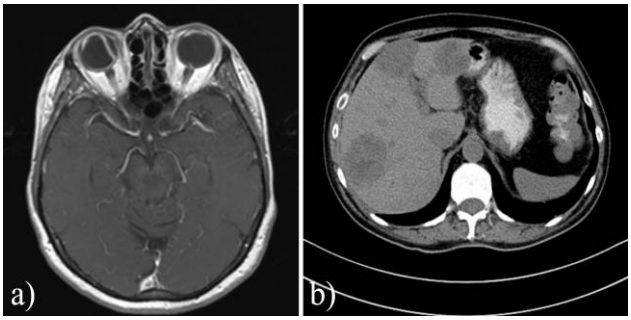

Figure 2. a) CT exam showing bilateral endophthalmitis with orbital cellulitis and retinal detachment in the RE; b) abdominal CT exam showing multiple hepatic abscess in the same patient

In both subgroups, the therapeutic approach combined 2 or 3 antibiotics from different classes (vancomycin, third generation cephalosporins, aminoglycosides, and/or ciprofloxacin). In cases of bacterial resistance to cephalosporins, a carbapenem was used by intravenous route. In 12 cases, metronidazole or piperacillin/ tazobactam was added for anaerobic pathogens. General fluconazole was administrated in 28 (50%) patients, with not significant differences between the two subgroups (40% vs 66.6%, p=0.08), in cases when the fungal etiology was proven, or could not be excluded based on anamnesis and clinical features.

Local therapy consisted of frequent topic administration of 2-3 antibiotics, steroids, cycloplegics, and anti-glaucomatous eye-drops in case of ocular hypertonicity. Intravitreal injections were used in 32 (57.1%) cases, with no significant differences between the two subgroups (p=0.44), and were associated with better outcome (p=0.03). Intravitreal drugs used were ceftazidime 2.25 mg/0.1 mL +/− vancomycin 1–2 mg/0.1 mL+/− amikacin 0.4 mg/0.1 mL, repeated according to clinical evolution at 48-72 hours, with a mean number 3.1±1.2 administrations. Vitrectomy was performed in 18 cases (32.1%), with slightly higher number of cases in the COVID-19 pandemic group (37.5% vs 25%, p=0.32).

In most cases, the vision was severely impaired by retinal detachment, persistent vitreous floaters, cataract, pupillary seclusion. The outcomes were similar in the two study subgroups in terms of mean hospital stay (p=0.06), and rate of evisceration or enucleation (p=0.17; Table 3).

Table 3. Outcomes in patients with acute endophthalmitis included in the study

Outcomes	Total group (n=56)	COVID-19 pandemic group (n=32)	Pre-pandemic group (n=24)	p-value
Evisceration/ Enucleation	10 (17.8%)	4 (13.33%)	6 (25%)	0.17
Final BCVA ≥0.1 CF HM LP No LP	 8 (14.2%) 11 (19.6%) 5 (8.9%) 7 (12.5%) 15 (26.7%)	 2 (6.25%) 7 (21.8%) 3 (9.3%) 4 (12.5%) 12 (37.5%)	 6 (25%) 4 (16.6%) 2 (8.3%) 3 (12.5%) 3 (12.5%)	0.001*
Death	1 (1.7%)	1 (3.1%)	0	0.67
Hospital stays	13.1 (± 4.62)	14.0 (± 5.88)	11.0 (± 5.11)	0.06
Footnote: * statistically significant				

The final visual acuity was worse in the Covid-19 pandemic (p=0.001). This may be explained by the differences in etiology between the two subgroups. In pre-pandemic group, there were more exogenous and postoperative endophthalmitis, while endogenous endophthalmitis was more frequent in the COVID-19 pandemic group, usually associated with poorer outcomes, due to more virulent organisms, immunocompromised host, and delay in diagnosis [3,4].

Discussions

Covid-19 pandemic was a major challenge for national healthcare systems and it had significantly the ophthalmology practice [11,13,14]. Repeated lockdown periods led to disruptions in ophthalmological appointments and limited accessibility. In our study, two patients presented recent COVID-19 infection. Although Sars-Cov 2 infection was reported to produce self-limited ocular manifestations, several reports showed an increase rate of endophthalmitis during Covid-19 pandemic [9-11].

Multiple mechanisms were taken into consideration to explain this finding. The mask wearing was considered by some authors to possibly increase risk of endophthalmitis after intravitreal injections, theoretically, through an upward direction of exhaled vapors toward the periocular area [15], other authors did not confirm this finding [16,17], emphasizing upon the importance of respecting the specific measure to increase perioperative patient's safety [18].

Several case-series raised the concern of increased rate of endogenous endophthalmitis in Covid-19 patients or in the post- Covid period, probably related to persistent immune suppression after Sars-Cov-2 infection, prolonged corticoid therapy and catheter wearing in severe cases [19-22]. We noticed in the pandemic group, for the first time cases of hypervirulent Klebsiella pneumoniae (hv Kp) endogenous endophthalmitis, with hepatic abscess in persons not previously known with any predisposing gastrointestinal condition. This new pathologic encounter was first reported in South East Asia 30 years ago, with worldwide dissemination of the hypervirulent strains of Klebsiella pneumoniae in the recent years [23-25]. In a single center study of Agi et col. [19], Klebsiella pneumoniae endogenous endophthalmitis was associate din 80% of cases with preceding COVID-19 infection, leading to the supposition that it may signal a new risk factor for KEE [19]. Other authors reported an increase incidence of fungal endophthalmitis in post-covid period [20-22].

Comparative statistical analysis showed a significant higher number of cases associated with systemic inflammatory reaction in the pandemic period, compared to the pre-pandemic group. This finding may be correlated with the higher incidence of endogenous endophthalmitis during the same period, taking into account that usually exogenous endophthalmitis is associated with a less significant systemic response [26]. Catheter bearing patients, either due to chronic renal disease or neoplastic diseases were more frequent associated with the endogenous endophthalmitis, due to multiple mechanisms including the existence of an entry site and disorders in immunity and defense mechanisms [27-29].

Another interesting finding is that, although only 8 (16.3%) patients were previously known with diabetes mellitus, with no significant differences between the 2 subgroups (p=0.44, Table 1), we found high a jeun glycemic values in 23 (44%) patients at admission, most of them belonging to COVID-19 pandemic subgroup (19 patients; 59.3%; p<0.001). Multiple studies showed solid evidences that diabetes mellitus is a significant risk factor for endogenous endophthalmitis, and for adverse prognosis [30,31]. Chronic systemic inflammation and poor glycemic control lead to impaired immune response, altered fibrin

network structure, while microvascular retinal damages favor increased capillary permeability [32-34]. One explanation may be related to the COVID-19 pandemic lockdown effects on the general population health, by delaying the regular check-ups on ambulatory basis [35-37]. Moreover, there are evidences for overall increased risk of new-onset both type 1 and type 2 diabetes (T2D) following COVID-19 infection [38-40].

Conclusions

During Covid-19 pandemic, there were specific changes in clinical characteristics and outcomes of acute endophthalmitis, including increased rate of endogenous endophthalmitis, delayed presentations, and poorer final visual acuity. Early diagnosis and prompt initiation of large spectrum antibiotherapy are essential to preserve vision.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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