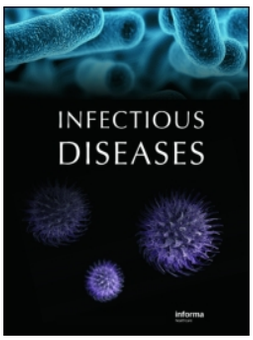

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ORIGINAL ARTICLE

Clinical characteristics and evaluation of the incidence of cryptococcosis in Finland 2004–2018

Anne Toivonen[a], Mari Eriksson[b], Nathalie Friberg[a], Timo Hautala[c], Sohvi Kääriäinen[d], Jaana Leppäaho-Lakka[e], Janne Mikkola[f], Tuomas Nieminen[g], Jarmo Oksi[h], Juha H. Salonen[i], Pekka Suomalainen[j], Markku Vänttinen[k], Hanna Jarva[l] and Annemarjut J. Jääskeläinen[a]

[a]HUS Diagnostic Center, HUSLAB, Clinical Microbiology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [b]Inflammation Center, Department of Infectious Disease, Helsinki University Hospital, Helsinki, Finland; [c]Research Unit of Biomedicine, University of Oulu and Department of Internal Medicine, Oulu University Hospital, Oulu, Finland; [d]Infection Control Unit, Seinäjoki Central Hospital, Seinäjoki, Finland and National Institute for Health and Welfare, Helsinki, Finland; [e]Central Hospital NOVA of Central Finland, Jyväskylä, Finland; [f]Department of Infection Control and Infectious Diseases, Kanta-Häme Central Hospital, Hämeenlinna, Finland; [g]Infectious Diseases Unit, Pori, Finland; [h]Department of Infectious Diseases, Turku University Hospital and University of Turku, Turku, Finland; [i]Department of Infectious Diseases, Vaasa Central Hospital, Vaasa, Finland; [j]Department of Infectious Diseases, South Karelia Central Hospital, Lappeenranta, Finland; [k]Infectious Diseases Unit, Department of Medicine, Kuopio University Hospital, Kuopio, Finland; [l]HUS Diagnostic Center, HUSLAB, Clinical Microbiology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland and Department of Bacteriology and Immunology and Translational Immunology Research Program, University of Helsinki, Helsinki, Finland

ABSTRACT

Background: Cryptococcosis is one of the major causes of mortality among HIV patients worldwide. Though most often associated with late stage HIV infection/AIDS, a significant number of cases occur in other immunocompromised patients such as solid organ transplant recipients and patients with hematological malignancies. Immunocompromised patients are a heterogeneous group and their number increases constantly. Since little is known about the incidence and the clinical features of cryptococcosis in Northern Europe, our aim was to investigate the clinical characteristics of cryptococcosis patients in Finland.

Methods: We retrospectively reviewed the laboratory confirmed cryptococcosis cases in Finland during 2004–2018. Only those who were treated for cryptococcosis were included in the study. Initial laboratory findings and medical records were also collected.

Results: A total of 22 patients with cryptococcosis were included in our study. The annual incidence of cryptococcosis was 0.03 cases per 100,000 population. Ten patients were HIV-positive and 12 out of 22 were HIV-negative. Hematological malignancy was the most common underlying condition among HIV-negative patients.

Conclusions: To our knowledge, this is the first study of the clinical presentation and incidence of cryptococcosis in Finland. We demonstrate that invasive cryptococcal infection occurs not only in HIV/AIDS patients or otherwise immunocompromised patients but also in immunocompetent individuals. Even though cryptococcosis is extremely rare in Finland, its recognition is important since the prognosis depends on rapid diagnostics and early antifungal therapy.

KEYWORDS
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CONTACT
Anne Toivonen
anne.toivonen@hus.fi
HUS Diagnostic Center, HUSLAB, Clinical Microbiology, University of Helsinki and Helsinki University Hospital, P.O. Box 720, Topeliuksenkatu 32, Helsinki 00029, Finland

Introduction

Encapsulated *Cryptococcus neoformans* and *Cryptococcus gattii* are the most common cryptococcal opportunistic fungal pathogens in humans [1]. The majority of cryptococcal infections worldwide are caused by *C. neoformans*, which occurs in most temperate regions whereas *C. gattii* has been found mainly in tropical and subtropical geographic regions [1,2]. Cryptococcus is transmitted by inhalation of infectious cells followed by an infection of the respiratory system. The pulmonary infection may disseminate by haematogenous route and further affect the central nervous system (CNS) causing meningoencephalitis [1]. The infection may also manifest as cryptococcemia, though the most common clinical features are meningoencephalitis and pulmonary cryptococcosis [3]. Moreover, a disseminated cryptococcal infection associates with higher mortality compared to respiratory disease [4]. However, the variable nature of clinical presentations may delay the diagnosis.

Although Cryptococcus is a rare cause of severe invasive infection in Northern Europe, cryptococcal meningitis is still one of the major causes of mortality among HIV-positive patients at the AIDS stage worldwide [5]. Immunocompromised individuals, particularly patients with impaired cellular immunity, are at the greatest risk. Although this infection is most often associated with advanced HIV, especially in the developing countries, a significant number of cases occur in non-HIV immunocompromised patients such as solid organ transplant recipients and those with hematological malignancies [3,6,7]. Moreover, the overall incidence of cryptococcosis is declining, but the group of non-HIV immunocompromised patients has become pronounced in recent years and is heterogeneous [4,6–9].

The incidence of cryptococcosis spans from a highest level in sub-Saharan Africa to the lowest in Western and Central Europe and in Oceania [10]. Less is known about the incidence or clinical features of cryptococcosis in Northern Europe, and in the Nordic countries in particular [11,12]. To our knowledge, only two clinical case reports of cryptococcal infection in Finnish patients have been published [13,14]. We had a hypothesis that cryptococcosis is most often diagnosed in HIV-positive immunosuppressed patients in Finland. For this purpose, we characterised retrospectively the clinical features and laboratory findings of cryptococcosis patients in Finland from January 2004 to December 2018.

Materials and methods

Subjects and study design

We retrospectively reviewed the microbiological laboratory results of Helsinki University Hospital Laboratory (HUS Diagnostic Centre, HUSLAB) from January 2004 to December 2018 serving over 1.6 million inhabitants of the total 5.5 million population of Finland. Clinical laboratories in other hospitals perform Cryptococcus antigen test screening in Finland followed by confirmation with cryptococcal culture in HUSLAB reference laboratory for fungal identification. This arrangement verifies high quality of microbiological diagnosis and gives an accurate estimation of the incidence of cryptococcosis in Finland. All patients with a positive serum and/or cerebrospinal fluid (CSF) antigen test and patients with *C.neoformans* culture positivity in CSF, blood or bronchoalveolar lavage (BAL) fluid were included in the study. In total 25 cases were found from laboratory records but our analysis of medical records was restricted to those 22 patients who underwent antifungal treatment directed at cryptococcosis. The patients' demographic and clinical data, including age, sex, ethnic background, underlying diseases, immunosuppressive medication, HIV status and possible antiretroviral therapy (ART), site of cryptococcal infection, antifungal therapy, clinical outcome, survival, cryptococcal antigen test results and culture results, initial leucocyte count, glucose and protein levels in CFS and blood CD4 cell count at cryptococcosis diagnosis were obtained.

HIV infection has been confirmed or excluded by a combined antibody-antigen test in a clinical laboratory at the time of the cryptococcosis diagnosis. AIDS stage was defined according to European Centre for Disease Prevention and Control (ECDC) criterion; at least one opportunistic infection regardless of the CD4 cell count [15].

This study was approved by the Helsinki University Hospital research ethics board (HUS/148/2017).

Laboratory analysis of C. neoformans *antigen*

Detection of *C. neoformans* antigen from serum or CSF was accomplished by using the agglutination based Pastorex™ Crypto Plus antigen detection kit for *Cryptococcus neoformans* (years 2004–2016; Bio-Rad, California, US) or Cryptococcal Antigen Lateral Flow Assay (CrAg LFA) (years 2017–2018; IMMY, Oklahoma, US).

C. neoformans from blood, CSF or BAL fluid culture samples was identified with ID 32 C Yeast Identification

System (bioMérieux, Marcy-l'Étoile, France) between 2004 and 2012 and from 2013 onwards by matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), (VITEK MS, bioMérieux). In some of the samples the identification of fungal species was confirmed also by panfungal PCR described earlier [16].

Statistical analysis

Descriptive analyses were performed to define the demographic and clinical characteristics of the study population. The crude incidence rate of cryptococcosis was calculated as follows: the sum of all cryptococcosis per year divided by the Finnish population. We expressed the annual incidence rate in Finland as cases per 100,000 population. The mortality rate was calculated as follows: the number of deaths at one year after the cryptococcosis diagnosis divided by the number of all cryptococcosis patients and expressed as percentage. The Mann-Whitney U test was used to compare medians of glucose and protein levels and the leucocyte cell count in CSF between HIV-positive and HIV-negative patients. *p*-values less than .05 were considered significant. The statistical analysis was performed with the GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, US).

Results

Clinical data

Table 1 summarises the demographic and clinical characteristics of all patients with cryptococcosis.

A total of 22 patients (12 males, 10 females, median age 52 y, range 27–18) were included in the study, corresponding to an annual incidence of 1.5 cases in Finland of 5.5 million population, which gives an approximate incidence of 0.03 per 100,000. All patients were treated in a central or university hospital in Finland. Sixteen patients were Finns, one was of other Caucasian origin and five were of Asian heritage .

Ten patients were HIV-positive and 12 were HIV-negative . None of the HIV-positive patients were receiving antiretroviral therapy (ART) at the time of the cryptococcosis diagnosis. Three HIV-positive patients had been previously diagnosed with HIV but refused ART. Seven patients were diagnosed as HIV-positive at AIDS stage at the time of the cryptococcosis diagnosis. All of the HIV-positive patients were diagnosed for cryptococcosis with CD4 cells less than 200×10^6/L (Table 2). Ten HIV-negative patients had some underlying immunosuppressive condition. Three of the HIV-negative patients suffered from sarcoidosis, five had a hematological malignancy, one had hypogammaglobulinemia for unknown reason, one had undergone liver transplantation and one had been diagnosed with granulomatotic polyangitis with severe renal failure. In addition, two patients had also renal insufficiency. Two patients (53 y and 76 y old) lacked underlying disease or medication affecting the immune system at the time of cryptococcosis diagnosis. The 53-year old patient had been diagnosed with idiopathic intracranial hypertension and had neurological symptoms. The 76-year old patient died and the only cause of death found in autopsy was cryptococcosis.

Table 1. The demographics and clinical data of the patients.

Characteristics	HIV-positive ($n = 10$)	HIV-negative ($n = 12$)	Total ($n = 22$)
Age (years) [median (range)]	42 (27–65)	61 (48–81)	52 (27–81)
Male gender	6	6	12
Finn	5	11	16
Other Caucasian	1	0	1
Asian	4	1	5
Underlying disease			
Hematological malignancy	0	5	5
Vasculitis	0	1	1
Sarcoidosis	0	3	3
Solid organ transplant	0	1	1
Hypogammaglobulinemia	0	1	1
Renal insufficency	0	3	3
Idiopathic intracranial hypertension	0	1	1
None	0	1	1
Immunosuppressive medication	0	9	9
ART	0	0	0
Clinical infection			
Meningoencephalitis	8	9	17
Cryptococcemia	2	1	3
Pulmonary disease	1	2	3
Focus not determined	1	0	1
Mortality			
1-year	3	2	5

ART: antiretroviral therapy.

The most common clinical manifestation of cryptococcosis was meningoencephalitis ($n = 17$). Three patients had pulmonary cryptococcosis. Two patients had both meningoencephalitis and cryptococcemia. One patient had cryptococcemia only. One patient had a positive serum antigen test without specified location of infection. This patient, however, had neurological symptoms and was treated for cryptococcosis.

The one-year mortality was 22.7%. Three of the HIV-positive patients and two of the HIV-negative patients died due to the cryptococcosis. The median time to death was 10 days.

A total 20 of the 22 patients were treated with antifungal therapy. One of the patients had been diagnosed for cryptococcosis but refused the medication and one

Table 2. Laboratory findings of the patients.

Variable	HIV-positive ($n = 10$)	p-value	HIV-negative ($n = 12$)	Total ($n = 22$)
Blood CD4+ T-cells (count x 10^6/L) [median (range)]	15 (3–150)		302 (55–750)	197 (3–750)
CSF glucose (mmol/L) [median (range)]	2.3 (1.5–5.2)	.82	3.0 (0.1–9.6)	2.5 (1.5–9.6)
CSF leukocyte cell count (10^6/L) [median (range)]	8 (0–238)	1.00	78 (0–225)	76 (0–238)
CSF protein (mg/L) [median (range)]	419 (155–1298)	.35	846 (201–1961)	665 (155–1961)
Positive serum cryptococcal antigen titre	5		8	13
Positive CSF cryptococcal antigen titre	4		7	11
Positive CSF Cryptococcus culture	4		7	11
Positive blood Cryptococcus culture	6		4	10
Positive BAL fluid culture	1		1	2

Normal values for laboratory parameters are listed as follows. Blood CD4 T-cells (10^6/L): 404–1612. CSF glucose (mmol/L): 2.3–4.3. CSF leukocyte cell count (10^6/L): 0–5. CSF protein (mg/L): 150–450 (14–60 y) and 200–600 (over 60 y).

died right after admission before onset of antifungal therapy. The antifungal therapy and its duration varied during the 15 year time period. The most common therapy was a combination of amphotericin B and fluconazole for the first weeks and fluconazole continued solely for a longer time.

Laboratory findings

The initial laboratory findings are shown in Table 2.

In 16 patients *C. neoformans* was found in fungal culture of CSF, blood or BAL fluid. Six of these patients showed positive CSF and blood cultures, five a positive CSF culture only and four patients a positive blood culture. One patient was diagnosed by BAL culture and the six remaining patients by CSF and/or serum antigen test. Eight of the patients showed positive CSF and serum antigen test, 11 a positive CSF antigen test and 13 a positive serum antigen test. The reference values of the antigen tests were ≤ 1 for the agglutination test (used 2004–2016) and ≤ 2 for the lateral flow test (used 2017–2018). Since the titre intervals of these two tests were different, further comparison was not accomplished.

The CD4 T cell count was available for 18 patients. The median CD4 count was 15×10^6/L (range $3–150 \times 10^6$/L) and 302×10^6/L (range $55–750 \times 10^6$/L) for HIV-positive and HIV-negative patients (reference value $404–1612 \times 10^6$/L), respectively. For seven of the eight HIV-positive patients with reported cell data the CD4 cell count was less than 100 cells 10^6/L. The median values of CSF routine examination among all patients were following: glucose level 2.5 mmol/L (reference value 2.3–4.3 mmol/L), protein level 665 mg/L (reference value for adults 14–60 years 150–450 mg/L and 200–600 mg/L for adults >60 years) and leukocyte cell count 76×10^6/L (reference value $0–5 \times 10^6$/L). There was no statistically significant difference between HIV-positive and HIV-negative patients.

Discussion

This retrospective case series evaluates the incidence and describes the clinical presentation of cryptococcosis in Finland where the HIV prevalence is low (an estimated 0.1%) [17]. By the end of 2018, Finland had registered 4044 of cases of HIV infection [18]. The crude annual incidence of cryptococcosis in Finland was 0.03 cases per 100,000 population. In comparison, in Sub-Saharan Africa, Asia and the Pacific region the annual incidence of cryptococcal antigenemia and prevalence of cryptococcal meningitis have been reported to be the highest, even up to 6–7%, of the population at risk for cryptococcosis while lower numbers have been reported in Europe, North America, North Africa, Middle East and the Caribbean [5]. Bitar et al. [19] have reported 0.2–0.5 cases per 100,000 population in France. However, the comparison of incidences is challenging since the studies have been based on various data or estimations. In Northern Europe, the incidence of cryptococcosis has been less studied. Mathiesen et al. [11] described 48 Danish patients with HIV-1-associated cryptococcal meningitis, with the majority of them diagnosed before 1997. In addition, Knudsen et al. [12] reported a nationwide survey of 28 cryptococcosis cases in Denmark in 1988–1993 with an incidence of 0.09 cases per 100,000, which is apparently higher than in our study. However, the majority of the cryptococcosis patient in the previous Danish studies have been diagnosed before the ART was recommended for all HIV patients.

HIV infection is still the most common underlying disease in patients with cryptococcosis, especially in developed countries. Similar findings have been reported in the United States, as up to 80% of the cryptococcosis cases are associated with HIV/AIDS [9,20]. Today the introduction of combined ART has changed the epidemiology of cryptococcosis, and fewer cryptococcosis cases are reported in HIV-positive patients [3,7,21,22]. In our study, an almost equal number of cases occurred in

HIV-positive ($n = 10$) and HIV-negative ($n = 12$) patients. However, the number of patients was too low to draw definite conclusions. In Finland, ART is accessible for all individuals with HIV infection, and the compliance for follow up and treatment adherence in general is good. Nearly half of the HIV-positive patients, in which CD4 cell count have been reported, have CD4 cell count less than 350×10^6/L at the time of diagnosis [18]. However, only a minority (an estimated 20%, personal communication) of the newly diagnosed HIV positive patients have CD4 cell count less than 100×10^6/L, which have been recommended as a screening cut off for cryptococcal disease [23]. Our data demonstrate that invasive cryptococcal infection is still one of the first HIV/AIDS defining diseases in a small amount of patients.

An increasing number of cryptococcosis has been reported in non-HIV infected immunocompromised patients such as solid organ transplant recipients and patients with haematologic malignancies, but also in patients with no immunocompromising conditions [3,7,23,24]. In our case series, the most common immunocompromising diseases, after HIV/AIDS, were haematologic malignancies and sarcoidosis. Only two patients, aged 53 and 76, were free from underlying disease or immunosuppressive medication at the time of the cryptococcosis diagnosis. The 76-year old patient died and the only cause of death found in autopsy was cryptococcosis. However, aging affects to the immune system and thus is one of the risk factors for severe clinical outcome of cryptococcosis. Usually a low cryptococcal antigen titre correlates with minor symptoms of clinical cryptococcosis specifically in non-HIV immunocompromised patients [25]. Since false positive results may appear especially in low antigen titres [26], the 53-year old HIV-negative patient treated for cryptococcosis without signs of disseminated infection but with neurological symptoms and a low positive antigen titre both in serum and CSF may, after all, be a false positive case. Correspondingly, high antigen titre has been reported to associate with disseminated cryptococcosis and a poor clinical outcome [25–27]. In our cohort, a CSF antigen test was done for only one of the five patients who died due to cryptococcosis, and the titre was high.

The laboratory diagnostics have been widely based on fungal culture and confirming the species by sequencing or, nowadays, by MALDI-TOF MS. Culture is relatively slow and the sensitivity is low (90% for CSF culture and 50–70% for blood cultures) [28]. Antigen tests are considered to be sensitive for the detection of the cryptococcosis in the early phase of infection but culture is the only method for testing the antifungal drug susceptibility [29,30]. In our study, more than half of the patients had a positive antigen test result in either serum or CSF. In majority of patients with a positive antigen test demonstrating of *C. neoformans*, infection was confirmed by blood, CSF or BAL-fluid culture.

Meningoencephalitis was the most common clinical manifestation both in HIV-positive and HIV-negative patients. In our case series, the most common antifungal therapy was a combination of amphotericin B and fluconazole since flucytosine has not been available in Finland. In HIV-positive patients, the antifungal therapy has been accomplished as recommended by the European AIDS Clinical Society (EACS) [31].

The one-year mortality was relatively low as only five out of 22 patients (22.7%) died of cryptococcosis. All of them had cryptococcal meningoencephalitis. In previous studies, the one-year mortality in Europe has been reported to be moderately higher, 25–35% [5]. In contrast to previous studies, which have reported the higher mortality among HIV-negative than in HIV-positive patients, we did not observe a difference between HIV-positive and HIV-negative patients. This may be caused by the lack of ART among HIV-positive patient as three of them had refused from the medication and the rest were diagnosed for HIV at the time of cryptococcosis and the ART was delayed as recommended by EACS [15]. The final outcome is not known for one our patients as they had moved from Finland before the one year follow up after the cryptococcosis diagnosis.

This study has some limitations. While HUSLAB serves as the confirmatory laboratory in cryptococcosis, other diagnostic laboratories may have carried out antigen tests during the study years, and some patients with minor symptoms may not be listed in the records. In addition, limited laboratory and medical records and travelling history were available for some patients due to the retrospective analysis. Since cryptococcosis is most often considered as HIV-associated disease the clinical suspicion may be delayed in non-HIV patients and thus some cases might be missed. This may further decrease the annual incidence. Only those patients who were treated as cryptococcosis were included in this study. We found only three other patients with positive culture or antigen test result and therefore the effect of the missing cases for the annual incidence is minor.

The antigen detection test does not separate *C. neoformans* and *C. gattii*, thus patients with cryptococcosis confirmed only by the antigen test may have had an infection caused by *C. gattii*. However, in the majority

(16 of 22) of the patients cryptococcosis was also confirmed by culture. During 2004–2018, the method of antigen test changed, although both antigen tests used in HUSLAB have shown similar sensitivity for detection of *C. neoformans* and *C. gattii*. The method for fungal identification from culture has changed as well but we assume that using the MALDI-TOF MS has improved the antifungal identification [32]. Moreover, the incidence rate was relatively constant during the 15 years.

Overall, this is the first study reporting the clinical presentation and incidence of cryptococcosis in Finland. The invasive cryptococcal infection occurred not only in HIV/AIDS or otherwise immunocompromised patients, but also in immunocompetent individuals. However, cryptococcosis is a rare disease in Finland, but it should be recognised as its prognosis depends on rapid diagnostics and introduction of antifungal therapy.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Jarmo Oksi http://orcid.org/0000-0002-3331-997X

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