

Cryptococcus's: An emerging infectious disease of global public health importance

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Pal M, Shuramo M, Gutama K et al. *Cryptococcus's*: An emerging infectious disease of global public health importance. *J Emerg Dis Prev Med*. 2022;5(3):41-43.

ABSTRACT

Cryptococcosis is an emerging deadly systemic disease caused by *Cryptococcus*, which is *basidiomycetous*, encapsulated yeast that occurs as a saprobe in nature. Only two species are known to cause disease from the genus *Cryptococcus*: *Cryptococcus neoformans* and *Cryptococcus gattii*. The source of infection is exogenous and the respiratory tract acts as the chief portal entry of fungus. The mode of disease getting from the contaminated environment is by inhalation of infectious fungal agent. An array of clinical spectrum of disease is reported in humans.

In immune-compromised persons, the disease has a significant morbidity and fatality rate. The direct demonstration and isolation of the pathogen in the clinical specimens still remains the gold standard of diagnosis. The fungus can be easily isolated from clinical samples of the patients on Pal sunflower seed medium. Several drugs, such as amphotericin B, *flucytosine*, *fluconazole*, *ketoconazole*, and *itraconazole* have been used for the treatment of the disease. Currently, there is no formal preventative technique or vaccination for *cryptococcosis*. Therefore, an early diagnosis and prompt treatment should be given to the patient in order to prevent mortality, particularly in HIV-positive individuals.

Key Words: *Cryptococcosis*, *Diagnosis*, *Emerging mycosis*, *Life threatening*, *Prevention*, *Public health*, *Treatment*

INTRODUCTION

Cryptococcosis is an infectious enigmatic important human and animal fungus disease that ranges from asymptomatic to life-threatening meningitis caused by *Cryptococcus* species [1]. *Busse Buschke's sickness*, *European blastomycosis*, *Torula meningitis*, or *Torulosis* are all names for *cryptococcosis*. The fungus prefers the lungs and the central nervous system, but it can also affect the skin, eyes, bones, joints, and prostate. *Cryptococcus* enters the body through the lungs [2]. At initially, the layer primarily impacted those who were immune-compromised, such as those with advanced HIV/AIDS disease, cancer patients, and organ transplant recipients. *Cryptococcus* causes difficulty breathing, cough, fever, and meningoencephalitis in people, which are primarily induced by inhalation of the infectious cells of the pathogen [3].

The disease is distributed throughout the world, but it is Latin America [4]. The disease primarily affects cats, but it also affects domestic animals such as dogs, cattle, sheep, goats, and horses, as well as wild animals. The main source of disease is considered the droppings of birds, particularly the pigeons [5]. The best way of diagnosis of *cryptococcal* infection is to culture samples directly from the diseased subjects on mycological media, especially the selective medium like Pal sunflower seed agar. It is difficult to eradicate the disease, as the organism is ubiquitously distributed in the nature. Due to a lack of diagnostic facilities in the laboratory, the condition has a high mortality rate in youngsters. As a result, prompt diagnosis is critical for disease control [6]. The main objective of this review is to raise public knowledge about this emerging fungal disease that is a global public health concern. more prevalent and causes more severe symptoms in Sub-Saharan Africa.

ETIOLOGY

The Genus *Cryptococcus* contained at least 37 different species, of which two species namely, *C. neoformans* and *C.gattii* are documented as an important pathogens that cause infections in humans and animals [7]. Occasionally, other species of *Cryptococcus* namely *C. laurentii* and *C. albidus* are also implicated in the etiology of disease. *Cryptococcus gattii* is an emerging global mycotic pathogen of humans and animals [8]. The organism is *basidiomycetous*, encapsulated yeast that is non-motile, gram-positive, and non-fermenting. Pigeon excreta, soil, bat guano, wood, parrot feces, munia bird droppings, other avian excreta, fruits, vegetables, wooden canary cages, nonpasteurized milk, *Eucalyptus* trees, and other avian excreta are all recognized as the sources of the fungus [9].

Recently, Pal has demonstrated the presence of *C. neoformans* in the air of an aviary by employing Pal sunflower seed medium.

TRANSMISSION

The fungus appears to be transmitted primarily through inhalation, but it can also enter the body through the traumatized skin [10]. The disease is spread by inhaling the infectious cells from the pigeon *feces-infested environment*. Nosocomial infection, and laboratory acquired are also recorded. The fungus does not spread from person to person or animal to animal [11]. The infected syringes, cannulas, or antibiotic preparations may be used to inject the organisms into the teat of the dairy animals. If the teat ends are not properly cleaned before therapy, it is very likely that fungus may enter the mammary gland and result in mastitis of the animals.

EPIDEMIOLOGY AND RISK FACTORS

Cryptococcosis is an emerging mycosis that is reported from many countries of the world including India. It is estimated that *cryptococcosis* is responsible for 625,000 deaths each year globally. Disease is encountered both sexes, all age groups in all seasons, and in immunocompetent as well as immunocompromised hosts. The persons who are occupationally exposed to avian excreta have a greater risk of acquiring the. *Cryptococcus neoformans* is found in the soil contaminated by avian excreta all over the world, while *Cryptococcus gattii* is found in tropical and subtropical nations, as well as in plants [12]. It is mentioned that HIV patients, cancer patients, organ transplant recipients, and immune-competent children are the main victim of the disease. In the mid-1980s, the disease became more common, with HIV/AIDS accounting for more than 80% of all *cryptococcosis* cases globally. Polysaccharide capsule is a virulence factor that inhibits the host immunological response and anti-phagocyte activity. It also has a thick cell wall, phenyl oxidase, phospholipase, and urease enzymes. Immune-compromised people, HIV/AIDS patients with CD4 counts of less than 200 per microliter, organ transplant and steroid therapy recipients, those traveling to a high-prevalence area, and professional employees who may be exposed to a polluted environment are highly likely to be affected by the disease. Although both *C. neoformans* and *C. gattii* can cause disease in apparently immune compromised hosts, *C. gattii* infections in such patients are much higher than *C. neoformans* infections [13].

PATHOGENESIS

The condition of the host defence, the virulence of the *C. neoformans*

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Received: 05-June-2022, Manuscript No. puljedpm-22-4950; Editor assigned: 09-June-2022, PreQC No. puljedpm-22-4950(PQ); Reviewed: 18-June-2022, QC No. puljedpm-22-4950(Q); Revised: 24-June-2022, Manuscript No. puljedpm-22-4950(R); Published: 28-June-2022, DOI: 10.37532/puljedpm.2022.5(3).41-43.



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The condition of the host defence, the virulence of the *C. neoformans* strain, and the size of the inoculum all play a role in the pathogenesis of cryptococcosis. The inhalation of infectious propagules (either poorly encapsulated yeast cells or basidiospores from environmental reservoirs) causes cryptococcal infection, which is then deposited in the pulmonary alveoli [14]. This yeast will often create a latent infection within the phagolysosome, with dormant (but viable) yeasts within the thoracic lymph nodes or a pulmonary granuloma that can last for years in an asymptomatic individual. When local immunity is weakened, the yeast can proliferate and spread outside of these pulmonary lymph node complexes, similar to the pathophysiology seen in reactivated tuberculosis or histoplasmosis [15].

CLINICAL SPECTRUM

The incubation period of cryptococcosis ranges from 15 to 30 days. Several clinical forms, such as meningeal, pulmonary, cutaneous, osseous and visceral are encountered in humans. The majority of disease symptoms in humans are non-specific. Meningitis and encephalitis are most commonly observed in immunocompromised individuals, with symptoms, such as nausea, headaches, and growth issues, as well as dementia, mental distress, and eyesight impairments.

In persons with a strong immune system, the disease has only a respiratory effect. If the disease is identified late in immune-compromised patients, the mortality rate can reach 30% [16].

DIAGNOSIS

A plethora of laboratory techniques, such as mycological, histopathological, immunological, and molecular are employed to make an unequivocal diagnosis of *Cryptococcus*'s. The pathogen can be easily demonstrated in the clinical materials by *Potassium Hydroxide* (KOH), *Gram stain*, *Nigrosine stain*, and *India ink* [17]. The impression smear from tissues can be easily stained by *Periodic Acid-Schiff* (PAS) technique. Several wide, circular, thickly encapsulated yeast cells with budding are demonstrated in the brain impression smear when stained by PAS method (Fig.1). The biopsied and autopsied tissues fixed in formalin are subjected to histopathology by using *Meyer's mucicarmine*, *Masson-Fontana*, *Periodic Acid-Schiff* (PAS), and *Alcian blue* methods to detect the fungus [18].

The culture of specimens can be attempted on selective medium like Pal sunflower seed agar that was developed by Pal in 1980, and later, it was simplified to make it a very cheap differential medium for an early laboratory diagnosis so that it can be widely employed by limited resource nations. The medium contained 45 gm of pulverized sunflower seed, 20 gm agar, 500 mg chloramphenicol, and 1000 ml of distilled water [19]. The diagnosis of cryptococcosis can be simply and quickly verified on this selective medium by looking for light to dark brown coloured colonies *C. neoformans* (Fig. 2). For the detection of antigen, lateral flow assay, latex agglutination and enzyme immunoassay are employed (WHO, 2018). Polymerase Chain Reaction (PCR) is also used in the diagnosis of [20].

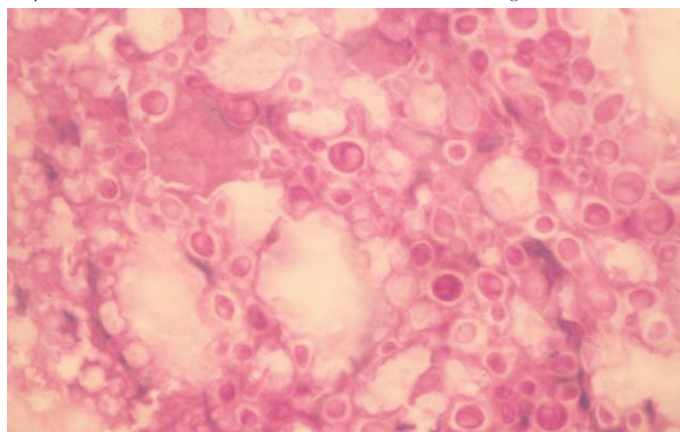


Figure 1. Impression smear from the mouse brain ten days after inoculation with *Cryptococcus neoformans* isolate from an AIDS patient, showing *Cryptococcus neoformans* with typical wide capsules. Periodic acid-Schiff \times 250.

Source: (Pal and Dave, 2006).

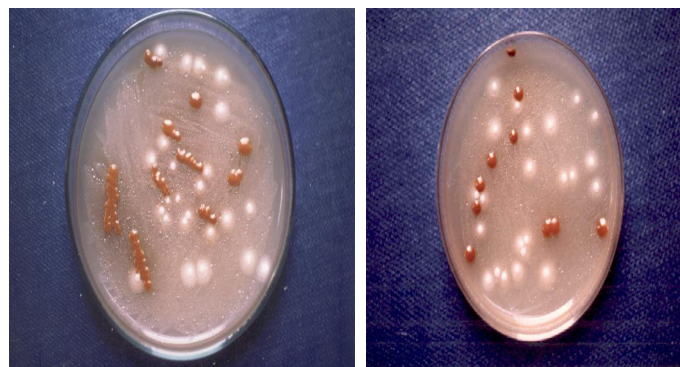


Figure 2: Many smooth, shiny, brown pigmented colonies of *Cryptococcus neoformans* on Pal sunflower seed medium after 8th days of incubation at 25°C. The pathogen was isolated from clinical specimens of a 79-year-old woman with lung cancer as an underlying disease.

Source: (Pal and Dave, 2006).

TREATMENT

Fluconazole, *itraconazole*, *flucytosine*, *ketoconazole* and *amphotericin B* are antifungal drugs that are recommended for the treatment of *cryptococcosis* (Pal, 2007; Dave and Pal, 2015; Pal and Dave, 2016) [21]. In order to decrease drug resistance, it is advised to use *flucytosine* with amphotericin in patients suffering from *cryptococcal* infection [22]. When the CNS and lungs are impacted during the induction phase of treatment, amphotericin B delivered intravenously in combination with *flucytosine* orally is the best treatment if the patient's kidney is healthy for two weeks. Fluconazole can also be used with *flucytosine*. After the patient has been treated with fluconazole or amphotericin B for two weeks, the fungal cultures are treated with fluconazole or amphotericin B for consolidation treatment. It is critical to continue fluconazole therapy for a year for as maintenance therapy [23]. It is pertinent to mention that negative culture of urine in male patients suggests effective treatment because prostate in male serves as reservoir of the fungus [24]. Recently, Dave and Pal (2015) successfully treated a case of primary cutaneous *cryptococcosis* in a parrot handler with fluconazole. The drug was given in the dosage of 200 mg orally daily for 14th weeks. The patient did not complain any side effects.

PREVENTION AND CONTROL

In summary, the current paper provides a psychological and neuroscientific description of working memory, including theoretical models of working memory, as well as neural patterns and brain regions involved in working memory in healthy and diseased brains. Working memory is thought to be the foundation for many other cognitive functions in humans, and knowing working memory mechanisms would be the first step toward understanding other parts of human cognition like perceptual or emotional processing. Following that, it would be reasonable to investigate the relationships between working memory and other cognitive systems [25].

It seems difficult to avoid the disease in areas where it is prevalent. It is tough because the infection is introduced through inhalation from the environment. It is critical to follow a doctor's or veterinarian's treatment instructions exactly [25]. The immunocompromised are advised not to visit the highly contaminated environment, especially the avian habitat. Any traumatic injury to the skin requires immediate medical attention. The avian excreta must be decontaminated by spraying 5 % formalin (Pal, 2007; Pal and Dave, 2016). In high-risk patients, active immunization in the form of a vaccine is an appropriate option for prevention. In mouse models, a cryptococcal GXM-tetanus toxoid combination vaccine has been created that looks to be highly immunogenic and elicits high-affinity IgG antibodies that appear to provide protection.

CONCLUSION AND RECOMMENDATIONS

Cryptococcosis is an enigmatic, emerging mycosis of humans and animals, and is caused by the species of the genus *Cryptococcus* that is ubiquitously prevalent in nature. The yeast typically affects the humans and animals with weakened immune systems. The environment, which has been contaminated by the feces of birds and plants, is the source of infection.

When the fungus is breathed, it causes lung infection and meningeal cryptococcosis, which is especially common in HIV patients.

As Pal sunflower seed medium is easily available, cheap, very specific, and sensitive for *C. neoformans*, therefore, it should be widely utilized in the public health and microbiology laboratories for the rapid isolation and identification of this zoonotic yeast from various types of clinical materials to confirm the diagnosis of disease to institute antifungal therapy to prevent the suffering of the patient.

Currently, no vaccine is available, and hence, sincere attempt should be made to develop a safe, potent and cheap vaccine that can be easily afforded by the low income countries to immunize the susceptible population. Additional research is needed on the ecology, pathogenesis, and epidemiology of cryptococcosis, a life threatening emerging mycosis of global concern.

ACKNOWLEDGEMENTS

We are thankful to Prof. Dr. R. K. Narayan for his critical suggestions during the preparation of the manuscript. The paper is dedicated to all the Scientists who did pioneer work in the field of cryptococcosis.

CONTRIBUTION OF AUTHORS

All the authors contributed equally. Each author read the final version, and approved it for publication.

CONFLICT OF INTEREST

There was no conflict of interest among the authors.

SOURCE OF FINANCIAL GRANT

There was no financial support from any organization for this manuscript.

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