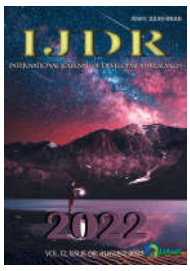
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 12, Issue, 08, pp. 58134-58136, August, 2022
https://doi.org/10.37118/ijdr.25109.08.2022



RESEARCH ARTICLE OPEN ACCESS

FUNGAL MENINGITIS: PATHOPHYSIOLOGY ASSOCIATED WITH CRYPTOCOCCUS SPP

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ARTICLE INFO

Article History:
Received 07th June, 2022
Received in revised form
23rd June, 2022
Accepted 27th July, 2022
Published online 22nd August, 2022

Key Words:
Cryptococcus, Immunosuppression, Meningitis, Pathophysiology.

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ABSTRACT

Meningitis are infections in the membranes that cover the Central Nervous System (CNS), known as leptomeninges, which are located in the subarachnoid space. Regarding fungal meningitis, there is a diverse group of causative pathogens, however this article focuses on the most common causative agent: Cryptococcus spp. Although the pathogenesis is still not fully understood, three mechanisms are able to cross the individual's blood-brain barrier, especially if the individual has a condition of immunosuppression. The methodology used is a literature review, using as a source the indexed articles, which were published between 2017 and 2022, the search descriptors chosen were: Cryptococcus, etiology, etiopathogenesis, pathophysiology and meningitis. According to the analysis of the 19 articles selected, it was noted that the infection affects differently according to the species of the fugus, for example, Cryptococcus neoformans can cause the occlusion of blood vessels and is linked to the condition of immunosuppression, while C. gatti is related to infections on immunocompetent individuals. Thus, cryptococcosis is considered the third disease caused by fungus, with the highest incidence in immunosuppressed patients, due to its neurotropism by the CNS, which can lead to severe meningitis, with rapid evolution and high mortality. Therefore, early fungal culture in case of suspected meningitis is important for choosing the best course of action, given the drug resistance of some species.

Citation: Maria Clara Oliveira Fernandes, Raquel Dutra Massad, Karla Gonçalves Godoy, Daniella Parron Ruiz de Carvalho et al. 2022. "Fungal meningitis: pathophysiology associated with cryptococcus Spp*", International Journal of Development Research, 12, (08), 58134-58136.*

INTRODUCTION

Meningitis are infections in the membranes that cover the Central Nervous System, known as leptomeninges (arachnoid and pia mater), which are located in the subarachnoid space (DE LIMA *et al*., 2021). In this sense, the impairment of this system causes numerous neurological and systemic manifestations, which can cause irreversible damage and death (ROLDI *et al*., 2022). This infectious disease, which has prevalence associated to the patient's age and immunity, the initial focus and also the local epidemiological situation, can result from invasion of the blood-brain barrier by various infectious agents, such as bacteria, viruses and fungi (DE LIMA *et al*., 2021). Regarding fungal meningitis, there is a very diverse group of causative pathogens, molds, dimorphic fungi, and yeasts, with Cryptococcus neoformans and Cryptococcus gatti (pathogenic encapsulated yeasts) being the most common causative agents in the world, especially in immunocompetent patients (PAL, 2017; CDC, 2018). Thus, the spores or dehydrated yeasts enter the patient's lung causing an infection, usually asymptomatic, and later, when passing through the patient's immune system, it reaches the Central Nervous System (ROLDI et al., 2022). In patients with immunosuppression, there is an increased permeability in the blood-brain barrier, thus facilitating the entry and multiplication of fungi, which promote the activation of nerve cells, the production of cytokines, chemokines resulting in inflammation of the brain tissue (GÓRALSKA *et al*., 2022). This disease is serious and has a high mortality rate (about 20 to 50% of affected patients) (ZARAGOZA, 2019). Although fungal infections of the Central Nervous System is still not fully understood, three mechanisms have been described,

which pathogens use to cross the blood-brain barrier after entering the parenchyma, they are: transcellular migration, paracellular migration and transport within macrophages, known as the Trojan Horse Mechanism (TENFORDE *et al*., 2018). Furthermore, the paracellular passage of C. neoformans between endothelial cells has also been described (GÓRALSKA *et al*., 2022). After the initial infection, patients begin to present signs and symptoms, such as: neck stiffness, prolonged fever, sweating, nausea and vomiting after eating, acute pain behind the eyes, significant weight loss and neurological deficits (TENFORDE *et al*., 2018). Although there are about 30 (thirty) species of cryptococci, only two of them are the main ones associated with pathologies, such as meningoencephalitis.

These fungi are able to invade the organism, replicate immediately or remain inactive for up to two years, waiting for a decrease of the immune system so they can invade (TENFORDE *et al*., 2018). Its spread usually occurs through the inhalation of fungal spores from the feces of animals, birds, mainly pigeons (rich in nitrogen sources, such as urea and creatinine). Pigeon infestation in some cities is a great risk of contamination (GÓRALSKA *et al*., 2022). In fungal meningitis, that is developed after inhaling these spores, the pathogen ends up colonizing the lung first, and this organ is often able to activate the immune system and effectively get rid of the pathogen (DE LIMA *et al*., 2021). However, in immunosuppressed patients for some reason, in particular those with defective CD4 T cells, this defense is weakened, it cannot prevent the invasion of the pathogen, which continues to cross the blood-brain barrier and reach the cerebrospinal fluid (ZARAGOZA, 2019). Before the emergence of HIV cases, the infection had a low incidence and was often a complication associated with other chronic diseases or the use of drugs, including those used to treat neoplasms, chronically used corticosteroids, immunosuppressants and chemotherapeutics. It is noted that research into the pathogenesis and virulence mechanisms of this pathogen has focused on three different areas: adaptation to the host environment (nutrients, pH and free radicals), immune evasion mechanisms (which include phenotypic variations and the ability to behave as a facultative intracellular pathogen) and production of virulence factors (ZARAGOZA, 2019). The treatment of choice recommended by the Infectious Diseases Society of America (IDSA), consists of a combination of amphotericin B deoxycholate (AmBd), 5-fluorocytosine, and fluconazole. (FIRACATIVE *et al*., 2018). Because this pathology affects immunosuppressed populations it is still overlooked and continues with a high mortality rate, the present research seeks to better understand its mechanisms, analyzing with the present research the pathophysiology of fungal meningitis associated with Cryptococcus, seeking to understand its invasion mechanisms of the immune system, epidemiology, prevention and treatment.

METHODOLOGY

The present study is a bibliographic review, using as a source the indexed articles, published between 2017 and 2022, in the Virtual Health Library (VHL), Google Scholar, U. S. National Library of Medicine (NLM) and Scientific Electronic Library Online (SCIELO). Articles that have the full text available in English and Portuguese were included. To perform the search on the platforms, the descriptors used were: Cryptococcus, Etiology, Etiopathogenesis, Pathophysiology, Meningitis. In the Google Scholar database, the option "Advanced search" was selected, having as a criterion the presence of all descriptors in the field "Anywhere in the article". In PUBMED, in advanced mode, articles from the last five years were filtered, using the "OR" filter between the descriptors. In SCIELO, the descriptors separated by the OR filter were selected in the "advanced search" option. From this first selection, a total of 1187 academic works were found, then, a more specific filtering was performed using as a parameter the reading of the title of each bibliographic material and the inclusion of those in which both descriptors were present or the relationship between meningitis and cryptococco infection. Thus, 30 productions remained. Finally, after reading the 30 abstracts of these articles, those that presented a content consistent with the objective of the work were selected, being therefore included 19 science papers that composed this study. For data analysis, the full reading of the articles was considered, so that the results indicate that the disease prevails in immunocompetent patients and the results associated in a late way evidence the demand for alternative methods for the study of the invasion of the immune system, epidemiology, prevention and treatment.

RESULTS AND DISCUSSION

According to the data obtained in the literature, we have an epidemiological profile of individuals affected by Cryptococcal meningitis, which is predominantly immunosuppressed, among which HIV carriers stand out (ZHAO *et al*., 2021). This corroborates the fact that such a pathology has a high mortality rate, which shows the essential need to understand the nuances of its pathophysiology (ZHOU *et al*., 2020). Infection with Cryptococcus neoformans can cause occlusion of blood vessels and lead to a hemorrhagic spread of the infection. Fungal cells, depending on their size, become trapped in the vasculature and proliferate resulting in vasodilation. Localized cryptococcal growth can lead to the loss of vessel integrity and its dissemination to the body (GIBSON *et al*., 2022). Among the species, we have C. neoformans, which is an opportunist fungi and linked to situations of immunosuppression patients, while C. gattii has studies of involvement in immunocompetent individuals in several endemic regions of South America, Northern Australia, Papua New Guinea, Africa and India (SOTO, 2021). In addition, cryptococcosis is considered the third disease caused by a fungus that most affects immunosuppressed patients, due to neurotropism by the CNS and then leading to severe and rapidly evolving meningitis (MARSILIO, 2018). Since it is a disease that has greater relevance in immunosuppressed patients, the most characteristic manifestations are acute, subacute or chronic meningitis or meningoencephalitis (GIBSON *et al*., 2022). Symptoms include headache, fever, altered level of consciousness, mental confusion, amnesia, amaurosis, convulsion, coma, photophobia and neck stiffness. As for the complications caused by the fungal agent, there are intracranial hypertension, hydrocephalus and less frequently cranial nerve palsy (SOTO, 2021). There are several virulence factors of C. neoformans that alter its susceptibility to antifungal drugs, such as cell wall melanization, polysaccharide capsule size, cell gigantism (titan cells) and transcriptional differences (GROSSMAN & CASADEVALL, 2017). Melanization and enlargement of polysaccharide capsules can increase resistance to amphotericin B and change susceptibility to fluconazole due to reduced permeability that blocks the entry of large molecules such as amphotericin B (VIEIRA *et al*., 2018). Titan cells, abnormally large polyploid cells, are less susceptible to high doses of fluconazole than typical cells. In addition, when exposed to the drug, they produce aneuploid offspring that are even more resistant to this antifungal agent (GIBSON *et al*., 2022). The study also suggests that despite the important role of macrophages in host defense, they have the potential to facilitate the dissemination of C. neoformans throughout the organism. This fungal cell is a facultative intracellular pathogen that can replicate within macrophages and overexpress genes with the potential to alter susceptibility to fluconazole and amphotericin B (GROSSMAN & CASADEVALL, 2017). It is known that Cryptococcus spp. It is characterized by a polysaccharide capsule containing cryptococcal antigen (CrAg) that surrounds its cell wall. CrAg is released into the biological environment during infection and constitutes a biomarker of cryptococcosis, which, although detectable, requires very expensive techniques to obtain (TEMFACK *et al*., 2021) Therefore, the poor results associated with late diagnosis emphasize the need for alternative methods and reliable for the timely diagnosis of this pathology (FRAZÃO, 2018).

CONCLUSION

As stated above, it is noted that infections by fungal meningitis are pathologies that affect the Central Nervous System (CNS) resulting in neurological and systemic dysfunctions. In addition, its prevalence

occurs mainly in association with the variables of age and immunity of the infected patient. Furthermore, there is a predominance of immunosuppressed patients in the manifestation of this disease, due to the rapid evolution and the involvement of a more severe form of the disease, which has a high mortality rate. Contamination occurs due to inhalation of spores from animal feces, which can lead to a systemic form because the fungus has the ability to lodge in the body, making the immune system unable to fight its invasion. In this sense, the most relevant species regarding the disease are Cryptococcus neoformans and Cryptococcus gatti, the first being the trigger for occlusions in blood vessels that can lead to a hemorrhagic spread of the pathology. Therefore, due to the physiological problems that these fungal species can cause in the CNS, their early diagnosis and appropriate therapeutic management is of fundamental importance for a favorable outcome and without the development of sequelae in individuals affected by this meningitis. Furthermore, due to virulence factors of the fungus (C.neoformans) that can modify the vulnerability of antifungal drugs, making it more resistant to drugs such as Fluconazole and Amphotericin B, there are difficulties in the treatment. Therefore, it is known that the study of the fungus, in case of suspicion of meningitis, is important for an accurate diagnosis, in which one can maintain an analysis of the origin of the disease and the best course of action to be taken.

REFERENCES

CDC. Centers for Disease Control and Prevention. C. neoformans Infection Statistics. Disponivel em: < https://www.cdc.gov /fungal/diseases/ cryptococco sis -neoformans/statistics.html >. Acesso em: 07 abr.2022.

De Lima, S. P. S., Guerreiro, M. R. A., de Jesus Maciel, A. R., Monteiro, J. C., da Silva, A. N. M. R., Vallinoto, A. C. R., ... & Feitosa, R. N. M. (2021). Meningite em pessoas vivendo com HIV: Aspectos clínico-epidemiológicos de casos em um hospital de referência no Estado do Pará, Brasil. Brazilian Journal of Health Review, 4(3), 11620-11638.

Firacative, C., Lizarazo, J., Illnait-Zaragozí, M. T., & Castañeda, E. (2018). The status of cryptococcosis in Latin America. Memórias do Instituto Oswaldo Cruz, 113.

Frazão, S. D. O. (2018). Avaliação da ocorrência de exocitose não-lítica em isolados clínicos de Cryptococcus spp.

Gibson, J. F., Bojarczuk, A., Evans, R. J., Kamuyango, A. A., Hotham, R., Lagendijk, A. K., ... & Johnston, S. A. (2022). Blood vessel occlusion by Cryptococcus neoformans is a mechanism for haemorrhagic dissemination of infection. PLoS pathogens, 18(4), e1010389.

Góralska, K., Blaszkowska, J., & Dzikowiec, M. (2018). Neuroinfections caused by fungi. Infection, 46(4), 443-459.

Grossman, N. T., & Casadevall, A. (2017). Physiological differences in Cryptococcus neoformans strains in vitro versus in vivo and their effects on antifungal susceptibility. Antimicrobial Agents and Chemotherapy, 61(3), e02108-16.

Marsilio, J. C. (2018). Criptococose em pacientes submetidos a transplante de órgãos sólidos: desenvolvimento da doença a partir de órgãos contaminados.

Moreira, L. A., Batista, S. C., Gritti, A., Silva, J. B. M., & Vido, M. H. C. (2017). Meningoencefalite causada por Cryptococcus neoformans em pacientes portadores de HIV/AIDS. Revista Educação em Foco, 9, 72-81.

PAL, Mahendra. Morbidity and Mortality Due to Fungal Infections. Journal of Applied Microbiology and Biochemistry. INDIA,2017. Disponivel em: < http://www.imedpub.com/ articles/morbidity-and-mortalitydue-to-fungal-infections.php ?aid =18314 .> Acesso em: 07 abr. 2022

Roldi, L. L., Vieira Filho, J. F. A., Ferrari, H. M., Sperandio, M. Q., Peichinho Filho, M. A. S., da Silva, M. G. G. N., ... & Guaitolini, A. C. (2022). Revisão bibliográfica: meningite bacteriana em adultos. Brazilian Journal of Development, 8(4), 24703-24710.

Rudnik, C. R. B., Alves, J. F., Merlos, P. G. C., & do Nascimento Lima, H. (2020). Achados Epidemiológicos de Neurocriptococose em Pacientes Imunocompetentes: Relato de Casos de um Hospital Público de Joinville, Brasil. Revista de Epidemiologia e Controle de Infecção, 10(3).

Soto, B. A. (2021). Perfil de pacientes com criptococose em hospital regional do interior de São Paulo.

Tenforde, Mark W. et al. Treatment for HIV□associated cryptococcal meningitis. Cochrane Database of Systematic Reviews, n. 7, 2018.

Vieira, Ricardo Parente Garcia, et al. "Cryptococcal Meningitis in Patient with Chronic Myeloid Leukemia." Health 10.10 (2018): 1349-1356.

Zaragoza, O. (2019). Basic principles of the virulence of Cryptococcus. Virulence, 10(1), 490-501.

Zhao, J., Weng, W., Chen, C., & Zhang, J. (2021). The prevalence and mortality of cryptococcal meningitis in patients with autoimmune diseases: a systematic review and meta-analysis. *European Journal of Clinical Microbiology & Infectious Diseases*, 40(12), 2515-2523.

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