

The clinical importance of neurocandidiasis: a literature review

A importância clínica da neurocandidíase: uma revisão da literatura

La importancia clínica de la neurocandidiasis: una revisión de la literatura

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RESUMO

A neurocandidíase neonatal é uma infecção fúngica rara, que apresenta altas taxas de mortalidade, e, quando não ocasiona o desfecho fatal, está relacionada a graves sequelas neurológicas. Acomete especialmente neonatos prematuros ou de baixo peso ao nascer. O aumento nas últimas décadas de parturição prematura e baixo peso predispõe ao possível aumento da neurocandidíase. Além disso, as infecções causadas pelo gênero *Candida* não se enquadram em doenças de notificação compulsória do SINAN, dificultando a criação de políticas públicas direcionadas ao manejo adequado. O seguinte estudo tem o objetivo de destacar a relevância clínica da neurocandidíase. Trata-se de um estudo exploratório, de caráter qualitativo, baseado nas bases de dados PubMed, Science Direct e Web of Science. Como resultado, houve uma amostra de 9 publicações, baseadas nos idiomas inglês e português, sendo distribuídas em pesquisas exploratórias, explicativas e revisões de literatura. Conclui-se que os austeros efeitos que a patologia gera nos neonatos, somado a elevada prevalência de infecções nosocomiais pela levedura, a inobrigatoriedade de notificação compulsória e a demanda de tempo considerável até o diagnóstico trazem a neurocandidíase a importância clínica devida na prática médica atual. Destaca-se, ainda, as limitações sobre a temática abordada, pela ausência de revisões sistemática e a literatura limitada.

Descritores: Infecções Fúngicas do Sistema Nervoso Central; Candidíase invasiva; Neonato.

ABSTRACT

Neonatal neurocandidiasis is a rare fungal infection with high mortality rates and, when not fatal, is associated with severe neurological sequelae. It particularly affects premature or low-birth-weight neonates. The increase in premature birth and low birth weight in recent decades predisposes to a possible increase in neurocandidiasis. Furthermore, infections caused by the *Candida* genus are not classified as diseases subject to mandatory notification by SINAN, hindering the creation of public policies aimed at appropriate management. The following study aims to highlight the clinical relevance of neurocandidiasis. This is an exploratory, qualitative study based on the PubMed, Science Direct, and Web of Science databases. As a result, there was a sample of 9 publications, based on English and Portuguese languages, distributed in exploratory, explanatory research and literature reviews. The conclusion is that the severe effects of the disease on newborns, combined with the high prevalence of nosocomial yeast infections, the lack of mandatory reporting, and the considerable time required for diagnosis, give neurocandidiasis the clinical importance it deserves in current medical practice. The limitations of the topic addressed are also noteworthy, due to the lack of systematic reviews and the limited literature.

Descriptors: Central Nervous System Fungal Infections; Candidiasis, Invasive; Newborn.

RESUMEN

La neurocandidiasis neonatal es una infección fúngica poco frecuente con alta tasa de mortalidad y, cuando no es mortal, se asocia con graves secuelas neurológicas. Afecta especialmente a neonatos prematuros o con bajo peso al nacer. El aumento de los nacimientos prematuros y de bajo peso al nacer en las últimas décadas predispone a un posible aumento de la neurocandidiasis. Además, las infecciones causadas por el género *Candida* no están clasificadas como enfermedades de notificación obligatoria por el SINAN, lo que dificulta la creación de políticas públicas para su manejo adecuado. El presente estudio busca destacar la relevancia clínica de la neurocandidiasis. Se trata de un estudio exploratorio y cualitativo basado en las bases de datos PubMed, Science Direct y Web of Science. Como resultado, se obtuvo una muestra de 9 publicaciones, basadas en los idiomas inglés y portugués, distribuidas en investigaciones exploratorias, explicativas y revisiones de literatura. La conclusión es que los graves efectos de la enfermedad en los recién nacidos, junto con la alta prevalencia de infecciones nosocomiales por levaduras, la falta de notificación obligatoria y el considerable tiempo requerido para el diagnóstico, otorgan a la neurocandidiasis la importancia clínica que merece en la práctica médica actual. Cabe destacar las limitaciones del tema abordado, debido a la falta de revisiones sistemáticas y la escasa bibliografía.

Descriptores: Infecciones Fúngicas del Sistema Nervoso Central; Candidiasis Invasiva; Neonato

Introdução

Candidiasis is a mycosis caused by the yeast *Candida* genus, with cutaneous, mucocutaneous, or disseminated involvement. The disseminated form, which involves hematogenous yeast invasion, is rare (approximately 2% of patients) and occurs primarily in immunosuppressed patients, newborns, and those with debilitating or neoplastic diseases¹. Of all the pathogens responsible for healthcare-associated infections (HAIs), the *Candida* genus ranks fourth, behind only other microorganisms of bacterial origin².

Among those classified as at risk, neonates stand out, especially those born prematurely and with low birth weight, accounting for 50% of cases of invasive neonatal candidiasis. According to the Ministry of Health, approximately 30 million births were recorded between 2012 and 2022, with more than 10% associated with prematurity, a number that has increased in recent decades³. In neonates, the organ most frequently affected by candidiasis is the central nervous system (CNS), constituting neurocandidiasis, which can even be present at birth, being designated as a congenital or late-onset infection. Invasion of the pathogen into the CNS results in high fatality rates, and even when it results in newborn survival, the newborn presents with severe long-term neurological sequelae, as the mycosis leads to apoptosis and necrosis of neuronal cells^{4,5}.

In 2022, the WHO published a list of priority fungal pathogens, divided into medium, high, and critical priority categories, to guide research, development, and public health actions. Among the agents listed, *Candida albicans* and *Candida auris* are classified as critical priority. However, despite the above, there is a lack of epidemiological data on these antigens⁵.

Thus, the main objective of this paper is to highlight the clinical importance of neurocandidiasis, since this disease does not have quantitative but rather qualitative clinical importance, given the neurological sequelae generated, the high percentage of neonatal deaths and the low monitoring of the health system regarding mycoses.

Method

This paper was an exploratory, qualitative study. Data were collected from original, comprehensive studies through a bibliographic survey. Articles published between 2021 and 2025 were selected to ensure greater contemporaneity. The research was conducted in the PUBMED, Science Direct, and Web of Science databases.

The descriptors used were selected from the health terminology consulted in the Health Science Descriptors (DECS), namely: "Fungal Infections of the Central Nervous System", "Invasive Candidiasis", "Neonate", using the connector "AND" between the descriptors. As an inclusion criterion, the search for open access articles, in Portuguese and English, included in the aforementioned period and with a thematic emphasis on neonatal neurocandidiasis in the studied sample, was defined. While articles outside the period established for the review, without consonance

with the thematic focus and duplicate articles were excluded. After describing the described method, the works were read and selected.

Results

A total of 9 publications were included in the study, with English being the predominant language (7 of the 9 selected articles), followed by Portuguese (2). Regarding the place of publication, Mexico (3 articles) had the highest rate, followed by the United States (2), and the remainder came from Germany, Brazil, Portugal, Italy, and Saudi Arabia. Regarding the study design, there were 5 explanatory studies, three literature reviews (narrative and integrative), and 1 exploratory study.

The process of analyzing the works to obtain the final sample was organized in Figure 1, a flowchart adapted from the PRISMA model.

The most recent article was in October 2024, and the oldest found was in June 2021.

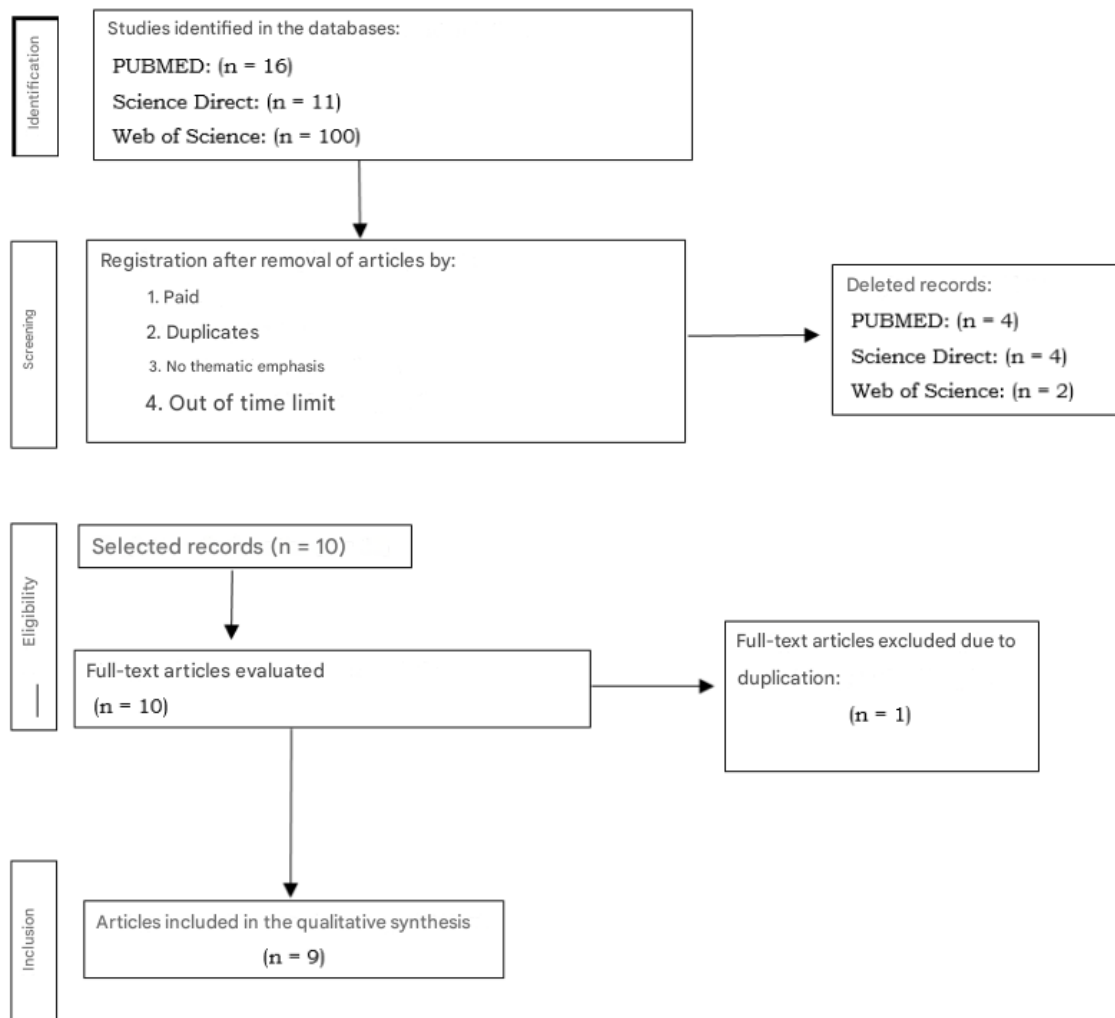


Figure 1 - Flowchart of bibliographic research and inclusion/exclusion criteria for the articles analyzed. (Source: Own authorship, 2025.)

Discussion

Based on the review, it was noted that the disseminated form of the *Candida* genus is rare, affecting approximately 2% of patients, a percentage primarily in neonates, especially those with premature birth and low birth weight, which accounted for 50% of cases of invasive neonatal candidiasis. Furthermore, 50% of neonates affected by the systemic form have fungal invasion of the central nervous system (CNS), which is associated with a 70% mortality rate⁴. Despite the high mortality rate, pediatric survivors when successfully treated, develop severe long-term neurological sequelae, including hydrocephalus, psychomotor retardation, and intellectual disability^{6,7}.

The clinical presentation of neurocandidiasis typically involves meningitis, meningoencephalitis, brain abscesses, and ventriculitis. In neonates, meningitis and brain abscesses due to fungal invasion of the brain parenchyma were the most common clinical manifestations and were commonly associated with fatal outcomes.

Through murine studies of disseminated neonatal candidiasis, the first site of fungus involvement was the meninges, followed by the forebrain, midbrain, and rhombencephalon. Histopathological analyses revealed frequent brain abscesses in these regions, resulting in cell death by necrosis and apoptosis. Thus, lesions in the forebrain, precursor of the cortex, thalamus, and hypothalamus are associated with cognitive alterations, while defects in motor control, respiration, and swallowing were observed in the midbrain and rhombencephalon. Furthermore, the clinical manifestations and cerebrospinal fluid (CSF) indices of patients with neurocandidiasis were similar to those of purulent meningitis, making their differentiation difficult in clinical practice. Imaging findings and culture results are crucial for clinical management.^{6,8,9,10,11}

However, the lack of rapid and reliable diagnostic methods poses another challenge in the approach to this pathology, as a positive culture is still considered the gold standard for diagnosing fungal diseases. However, this method has a low sensitivity rate (21-71%), requires a long time to obtain results (2-5 days), and is affected by multiple factors, such as the location and time of sample collection. Therefore, more advanced diagnostic techniques, such as mass spectrometry, molecular methods, or serological tests, are required for an accurate diagnosis^{5,10,11}.

Furthermore, the exemption from mandatory reporting of candidiasis cases to SINAN hinders the development of an epidemiological profile of neurocandidiasis and, consequently, awareness of the vulnerability of the neonatal population. This hinders the development of more effective antifungal agents with greater CNS penetration, given that amphotericin B deoxycholate or liposomal amphotericin B, first-line therapies for fungal infections in neonates, have limited use due to the risk of nephrotoxicity⁹. Regarding fluconazole, a second-line medication, some fungal strains have already developed resistance to the drug. In order to remedy these complications, the implementation of micafugin, an

echinocandida, is being studied. It appears to be effective against fluconazole-resistant strains and crosses the blood-brain barrier at therapeutic levels. However, despite its approval by the European Medicines Agency (EMA), the limited data available on the efficacy and safety of the drug in pediatric patients still partially restrict its clinical use⁷.

Thus, when not associated with a fatal outcome, these infants present severe long-term neurological impairment. Furthermore, the presence of nonspecific symptoms - leading to misdiagnosis -, the lack of a rapid and accurate diagnostic method, the lack of mandatory reporting to SINAN, and the inherent resistance of certain fungi to available antifungal agents and their limited penetration into the CNS , all contribute to and corroborate the clinical relevance of neonatal neurocandidiasis.

Final Considerations

In short, neonatal neurocandidiasis is one of the manifestations of invasive candidiasis in pediatric patients. It is not quantitatively significant, given its low incidence, but rather qualitatively significant, given its high mortality rate. When not fatal, children experience severe long-term neurological sequelae. Furthermore, the lack of specific clinical manifestations and a more sensitive diagnostic method, in addition to the lack of mandatory reporting to SINAN, undermine the pathology's adequate importance in today's context.

Therefore, this paper aims to give neurocandidiasis the qualitative and clinical relevance it deserves. Factors such as the lack of a systematic review on the chosen topic and the limited literature were limitations to the study; therefore, for future research, more exploratory analyses, such as integrative and systematic reviews, are recommended.

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