A Current Review of Neurological Effects of Cryptococcal Meningitis Infection in HIV-Positive Individuals

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Abstract

Cryptococcal meningitis (CM) is one of the most common fungal opportunistic infections affecting HIV-positive individuals. Viral infection is caused by exposure to ubiquitous encapsulated yeast *Cryptococcus* neoformans through the inhalation of basidiospores or yeast cells. Potential sources of infection include soil or avian droppings. The disease is characterized by a low CD4 T cell count, high intracranial pressure, and other neurological clinical symptoms including headache, sensitivity to light, stiff neck, and altered mental status. Most notably, it affects the lungs and central nervous system of immunocompromised HIV-positive individuals, which can lead to a variety of neurological manifestations and be the defining event of an AIDS diagnosis. HIV-positive CM is most prevalent in areas such as sub-Saharan Africa due to limited resources so investigations into antifungal treatments such as antiretroviral therapy demonstrate a lack of effect. New point-of-care screening methods such as a lateral flow cryptococcal antigen assay must be explored to counteract this effect. Aggressive management may also be utilized as a more invasive approach to control increased intracranial pressure, which is one of the main causes of neurological symptoms associated with cryptococcal meningitis. A lack of timely treatment and monitoring of intracranial pressure accounts for much of the morbidity and mortality associated with this disease. This narrative review utilized various sources and databases of peer-reviewed articles that were most up-to-date and relevant about evaluating the current findings of neurocognitive effects of cryptococcal meningitis infection in HIV-positive individuals, along with advancements in clinical management and drug therapy.

Introduction

HIV, human immunodeficiency virus, is a transmissible viral infection that damages the body's immune system and weakens its ability to fight infection and disease (1). By targeting CD4 T cells, a type of lymphocyte integral in immune response coordination, HIV infection increases an individual's susceptibility to opportunistic infections, such as fungal cryptococcal meningitis (CM) and bacterial infections (2). Bloodwork determining an individual's CD4 T cell count is a key metric in HIV disease progression evaluation and can play a central role in a host of clinical decisions such as when to initiate antiretroviral therapy (ART) (2). CD4 T cell count monitoring is also central in assessing an HIV-positive individual's risk for opportunistic infection and can aid in infection diagnostics, identifying which prophylactic(s) should be administered and treatment onset (2,3). The normal range of CD4 count is from 500 to 1,500 cells/cubic millimeter of blood (4). If the number of CD4 cells in a person's blood falls below 200 cells/cubic millimeter of blood, their immunity is weakened and can lead to acquired immunodeficiency syndrome (AIDS) (4). The immune system is severely damaged in AIDS and is susceptible to fatal infections or cancer (5). It is estimated that in 2021, 38.4 million people are living with HIV worldwide and 650,000 people died of HIV-related illnesses (4).

CM is a type of meningitis that often affects people who have HIV and is one of the most prevalent opportunistic infections that can occur in people with AIDS (6). HIV-associated CM is a significant complication in HIV-positive individuals and is an AIDS defining illness especially in environments with limited resources, and accounts for up to 15% of overall HIV-related deaths (7). There are approximately 152,000 cases of CM that occur among people with HIV/AIDS worldwide each year, resulting in an estimated 112,000 deaths (7). Outcomes can be poor, with the most significant burden of the disease in sub-Saharan Africa and Southeast Asia (8). Despite the observed overall decrease in CM incidence over the years, improvement in the health and mortality of individuals with this infection should remain a necessary public health goal to aid in decreasing the global disease burden.

Disease presentation of CM is usually acute, with a gradual increase in fever, malaise, and headache (9). These symptoms can sometimes be associated with neck stiffness, photophobia, vomiting, confusion, and a decreased level of consciousness (9). Clinical symptoms evolve as the infection progresses, eventually including nausea, photophobia, visual obscurations, diplopia, meningismus, and encephalopathy (10). These symptoms could be a sign of increased intracranial pressure (ICP), and a neurologic examination can be performed to assess signs of papilledema, defined as bilateral optic disc swelling induced by intracranial hypertension and additional cranial neuropathies (10).

CM is most commonly caused by the ubiquitous encapsulated yeast *Cryptococcus neoformans* (10). Exposure occurs through inhalation of the basidiospores or yeast cells from soil or avian droppings (11). *C. neoformans* can establish an innate immune response within the lungs through phagocytes like macrophages or cause pulmonary disease (12). Following inhalation, the cell wall components of cryptococcal cells are recognized by receptors in the immune system, which triggers the innate immune response (13). This response includes the phagocytosis of alveolar macrophages and the formation of granulomas (12). The mode of infection is characterized as the "Trojan horse" approach, which involves *C. neoformans* hiding inside white blood cells, such as macrophages, monocytes, and neutrophils (14). These cells act as a reservoir for *C. neoformans*, shielding the fungus from the body's immune system, which can help promote latent infection or persistent chronic inflammation (14,

15). The latent infection can then be distributed to the CNS, cross the blood-brain barrier (BBB), and infect the meninges, leading to cryptococcal meningitis as seen in Figure 1 (11).

Limited research has been conducted on the neural mechanism of how this fungus survives in the brain once it crosses the BBB. Several studies have explored how *C. neoformans* can survive in a nutrient-poor environment in the CNS and brain (16). These studies suggest that this organism adapts to host-specific signals and can modify immune responses while spreading into the CNS (16). Additional study has shown that *C. neoformans* forms melanin via substrates, including diphenolic compounds such as epinephrine, dihydroxyphenylalanine (DOPA), and norepinephrine (17). The enhanced accessibility of these neurotransmitters in neural tissue has been suggested as a potential explanation for the neurotrophic properties of *C. neoformans* (16).

There has been a reduction in the estimated total global burden of HIV-associated CM since 2014, likely due to antiretroviral therapy (ART) expansion and improved screening programs (7). However, much remains unknown regarding CM's long-term neurocognitive and neurological effects in HIV. Analysis suggests that neuroradiological data is limited to case reports and small case studies from developed countries (18). Studies so far show that neuroradiological lesions related to CM include dilated perivascular spaces, pseudocysts, cryptococcosis, basal meningitis, and hydrocephalus (19). Seizures were also common among patients with HIV-associated cryptococcal meningitis and were associated with decreased neurocognitive function and survival (20). Still, further research needs to be completed in countries where the disease burden remains high, primarily those in the sub-Saharan African region that experience the effects of limited resources and suboptimal health care. Although substantial research is currently focused on an increased understanding of disease pathogenesis, there is a lack of emphasis placed on the understanding of mechanisms underlying disease development in the brain. This narrative review evaluates the neurological effects of cryptococcal meningitis infection in HIV-positive individuals, advancements in clinical management, point of care, and novel drug therapy regimens.

Methods

A literature search was performed and utilized various sources and databases while evaluating the neurocognitive effects of cryptococcal meningitis, including PubMed and Google Scholar. No date range or journal exclusion was applied; however, priority was assigned to manuscripts published in or after 2010. The following key terms were used to find relevant articles: "cryptococcal meningitis," "cryptococcal meningoencephalitis," "HIV-associated meningitis," "opportunistic infections," "fungal infections," or "cryptococcus neoformans" in combination with "neurological effect," "neurocognitive effect," "antiretroviral," "therapy," or "treatment," and "therapeutic lumbar puncture meningitis," or "cryptococcal meningitis neuroimmunology" or "clinical considerations for cryptococcal meningitis" or "shunting in cryptococcal meningitis" or "ICP in meningitis" or "clinical standards for ICP." These papers were peer-reviewed and were among the most up-to-date and relevant articles pertaining to these queries. The mechanism of *Cryptococcus neoformans* figure was created using a website called BioRender.

Discussion

Relationship Between Cryptococcal Meningitis and HIV

Opportunistic Infections

Opportunistic infections (OIs) can become pathogenic when the functioning of the body's immune system is suboptimal (21). The four main types of OIs are bacterial, parasitic, fungal, and viral. When these pathogens take advantage of the weakened immune system, they can harm one's health by causing unusually severe diseases. Since these microbes typically inhabit environments other than human hosts, once they enter a human body, the transmission depends on human-to-human contact to continue the spread (22). Transmission can occur through various mechanisms, including airborne, aerosol, respiratory droplets, vector-borne, fecal-oral, and direct or indirect contact. OIs are considerably associated with morbidity and mortality and can arise from an altered microbiota, a breached epithelium, and, most notably, an already weakened immunity (23).

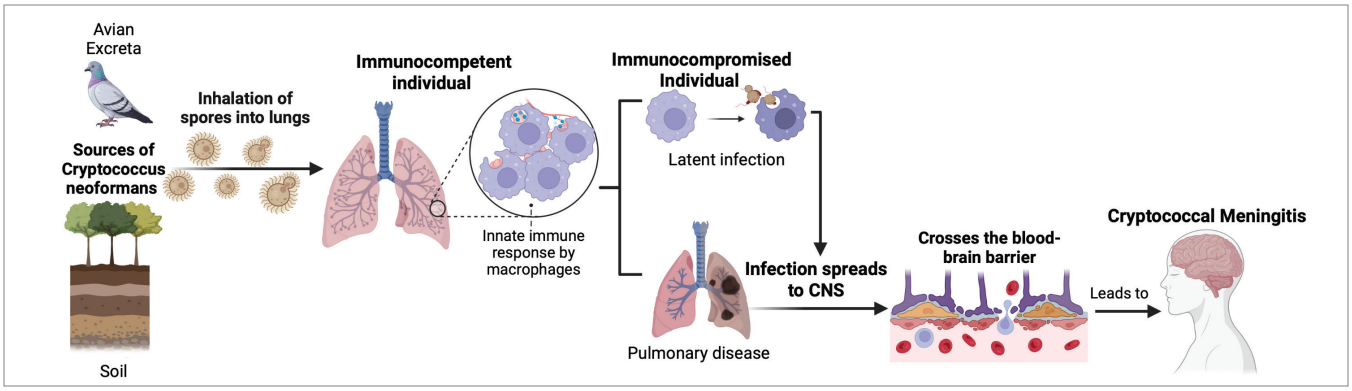

Figure 1. Summary of *Cryptococcus neoformans* mechanism of infection. Common sources of *C. neoformans* are soil and avian excreta. The portal of entry is through the inhalation of spores into the lungs. In an immunocompetent individual, the innate response uses cells like macrophages to phagocytose this pathogen and secretes pro-inflammatory mediators to eliminate the infection. In contrast, in an immunocompromised individual, like an HIV-infected individual, the immune system cannot fight off the infection, thus leading to pulmonary disease or a latent infection that will be reactivated later. The infection then spreads to the CNS, crosses the blood-brain barrier, and leads to cryptococcal meningitis. This figure was created using biorender.com.

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) is an infection characterized by a viral attack on the body's immune system (24). There are two versions of HIV: HIV-1, which is more often associated with OIs, and HIV-2, which is less common. HIV-1 is a single-stranded, positive sense ribonucleic acid (RNA) virus that infects a host's genome by transcribing viral RNA into deoxyribonucleic acid (DNA) and replicating it (25). The three main stages of HIV are the acute primary infection stage, the asymptomatic or latent stage, and the symptomatic chronic illness stage. The progression of the disease between each stage varies from person to person. The clinical manifestations of the acute infection stage can last between 3 and 25 days and may include general symptoms such as fever, fatigue, weight loss, headaches, myalgias, vomiting, and diarrhea (26). HIV can affect the body's systems, such as cardiac, ocular, gastrointestinal, and neurologic systems.

Cryptococcal Meningitis and HIV

OIs are often present in the third stage of HIV infection, as a positive individual is at a higher risk and is more susceptible to complications due to their immune system (7, 27). In the majority of cases, the presence of more than 20 OIs is also seen as the AIDS-defining event of a patient living with HIV. Although the number of OIs in HIV patients has decreased in developed countries, they remain a source of hospitalization and death in these areas despite improvements. More importantly, a reduction in OI incidence has not been established in resource-limited regions, such as in sub-Saharan Africa, where communities struggle with late diagnoses and poor access to treatments (7, 28). The predominant type of OI seen in HIV patients, especially in more advanced cases or during the third stage, are CNS OIs, as a favorable environment is created by the combination of a high HIV load and diminishing immunity (25).

The most common CNS fungal infection in HIV individuals is CM, which can prove fatal within three months of the disease onset (26, 29, 30). Both computerized tomography (CT) and magnetic resonance imaging (MRI) brain scans can aid in evaluating cryptococcomas, meningeal inflammation, vasculitis, and ventricular compression (31). To diagnose cryptococcal meningoencephalitis definitively, a cerebrospinal fluid (CSF) sample must be obtained via lumbar puncture (LP) and examined for signs of infection. A patient's opening CSF pressure should also be measured as raised intracranial pressure is common and may necessitate therapeutic CSF drainage management (9). CSF culture remains the gold standard for CM diagnosis; however, definitive results may take one to two weeks, and often, patients' analyses demonstrate normal CSF levels (7, 29). Two novel diagnostic methods that may be used are India ink microscopy, a more efficient test, and cryptococcal antigen testing (CrAg), which is highly specific and more sensitive than the CSF culture, with the ability to detect CM in the blood weeks to months before the onset of symptoms (18, 28, 29). Additional diagnostic features may include clinical presentation of symptoms, temporal evolution, and both CSF and radiographic findings, along with a CD4+ cell count of lower than 200 cells per microliter (25, 30). Universal symptoms may include headache, nausea, fever, discomfort, and seizures, and these acute signs may present concurrently for up to three weeks (29, 30, 32). Vision-related complications include diplopia, papilledema, photophobia, and reduced visual acuity.

A key neurologically-based manifestation that arises in CM infection is hydrocephalus in combination with increased intracranial pressure that may bring rise to encephalopathic symptoms such as memory loss, altered behavior, lethargy, and personality changes (25, 29). Other neurological indications include cryptococcomas or mass lesions and accumulation of cysts in Virchow Robin (VR) spaces, which are the spaces that surround blood vessels of the brain and cranial nerves (25, 32). Neurological findings included detections of basal meningeal enhancement, hydrocephalus, cerebral infarcts, cryptococcomas, and pseudocysts or VR space dilatation.

One study compared two groups of HIV-positive patients with CM, where one group was classified as young adults (≤40 years), and the other group was classified as older adults (>40 years) (33). The study found that older patients initially experienced headaches, fevers, seizures, visual disturbances, and hearing impairment. It also determined that younger patients presented with a higher incidence of headaches as the primary manifestation, which may be due to increased ICP found in the young adult group. An additional study analyzed brain lesions from radiological brain images of HIV-positive patients with CM, utilizing both CT and MRI imaging (35). Radiological findings at baseline found upon CT interpretation included pseudocysts, hydrocephalus, edema, intracerebral masses, dilated VR spaces, and radiological meningitis, while radiological findings at baseline upon MRI interpretation were intracerebral masses, pseudocyst, dilated VR spaces, meningitis, perilesional edema, as well as nodules or masses in the frontal and occipital lobes, parietal gyri, basal ganglia, and the corpus callosum (35). Although MRI imaging proved more accurate in determining brain lesions, both scans showed abnormal brain imaging that could be linked to poor prognosis and increased fatality from the time of diagnosis of CM.

Cryptococcal Meningitis in HIV-Positive Children

The vast majority of research executed regarding CM in HIV-positive individuals has solely included adult patients, therefore, little is known concerning infected patients who are under the age of 18. The previously cited study concerned with the clinical characteristics of CM in a younger demographic found that younger patients had a higher incidence of headaches due to higher intracranial pressure and a better clinical outcome at discharge and after a year of follow-up (33). However, even in this study, young adults were classified as patients who were 40 years or younger. Another study followed 19 patients in the age range of 4.8–10.8 years, and they presented with basic clinical symptoms of fever, headaches, nausea, abdominal pain, dyspnea, and seizures (35). The primary neurologic sign described in this age group was meningeal irritation that included pleocytosis and increased CSF protein levels, with no focal neurologic signs being recorded.

A third study investigated children under the age of 16, and the main neurologic abnormalities found were hypodensities, hydrocephalus, calcifications, masses, an increase in meningeal enhancement, and cerebral hemorrhages (36). Nevertheless, this same study described the low frequency of CM in HIV-positive children, citing that there were less than 1,000 cases of CM in children discussed in worldwide literature as of 2012. The reason for this occurrence remains unknown, but a potential explanation may be that children have antibodies against *Cryptococcus* species that were gained from exposure to

fungus and infections during their childhood. Overall, research focused on HIV-positive pediatric populations infected with CM is minimal, and despite low incidence, can serve as a source for further investigations in the future.

Antifungal Treatment

Evidence supports poor outcomes regarding the long-term effects of antifungal treatment, attributing them to late presentation, lack of access to medications, and monitoring (37, 38). Furthermore, a lack of adherence and retention, which are common in HIV care, is causing a lack of decrease in CM incidence despite the availability of antiretroviral therapy (ART). Nonetheless, detection technique advancements have improved outcomes by providing the option of earlier screening, diagnosis, and treatment (38).

Research focused on improving ART has demonstrated impressive feats and continues to update medication regimens and monitor availability to allow better access for patients in low-resource areas. Currently, the combination of Amphotericin B and flucytosine is the regimen of choice, having shown a higher survival advantage over Amphotericin alone, in conjunction with faster clearance of infection (38). However, the 14-day regimen of amphotericin B poses challenges for low-resource clinics due to prevalent adverse effects such as renal impairment, hypokalemia, hypomagnesemia, and anemia (39). The Center for Global Health in the United Kingdom has continued to make strides with regard to treatment standards, finding comparable results with high doses of fluconazole and flucytosine with one week of amphotericin B. This new regimen would be more readily available and safer to use in areas with limited resources while also being associated with low mortality (40). Other medications have shown reputable results, as previous studies have explored that an additional dose of sertraline can increase early fungicidal activity and show a decrease in relapse (41). The most current research showcases a new medication called Viamet 1129 (VT-1129), which has shown promising efficacy in CM murine models with plans for further studies and clinical trials (42).

In considering the ART regimen associated with the best outcomes, it is essential to appreciate other symptoms that could be detrimental if not closely monitored. Increased intracranial pressure and raised levels of CSF are associated with additional manifestations and worse outcomes (38). Immune reconstitution inflammatory syndrome (IRIS) is a newly recognized complication after initiating ART therapy. The manifestations of CM-associated IRIS include a paradoxical worsening of CNS symptoms and the unmasking of disease in organs not previously recognized to be affected (38). Improved CSF value monitoring can reduce high mortality rates, thus permitting earlier antifungal treatment and reduction of poor outcomes (43).

Changes to Point-of-Care

When considering point of care in resource-limited settings, regimens that require a shorter hospital stay and are better tolerated need to be considered. A phase III trial was completed exploring the use of high-dose liposomal amphotericin B (AmBisome), showing comparable results to the standard ART regimens (37). Having shorter regimens will allow the patients to have more flexibility in their care, therefore increasing adherence to treatment and improving subsequent responses and outcomes. The Infectious Disease Institute of Makerere University in Kampala, Uganda, has endorsed community engagement as having positive effects on trial referrals, drug adherence, and reduction of missed visits (43). Reiterating the importance of more manageable treatments in tandem with strong community support.

In recent years, simple lateral flow assays (LFA) for CrAg have been developed. These are inexpensive and provide rapid results when performed on CSF, serum, or urine. The immunoassay (IMMY) lateral flow test has a high sensitivity for detecting *Cryptococcus* in CSF of HIV-infected patients and has become the foundation of diagnosis in screen-and-treat programs (44). LFA is a test that uses two different types of antibodies to identify cryptococcal infections (44). It is very sensitive and can identify both *C. neoformans* and *C. gattii* species complexes (13). The IMMY CrAg LFA is also a low-cost, rapid, easy-to-use test, which is an advantage for limited resource environments (13).

Role of Invasive Therapeutics

Raised Intracranial Pressure Management

Despite mortality of individuals with concurrent human immunodeficiency virus and cryptococcal meningitis infection being as high as 78% one year post-CM diagnosis, people living with HIV/AIDS (PLWH) who survive *C. neoformans* infection are at increased risk for suffering from lifelong sequelae, including long-term morbidity primarily due to both cognitive, visual, and auditory impairments (45, 46). The role of ancillary therapies in effectively addressing raised ICP caused by CM and adequately controlling neurological and sensorineural sequelae is a vital consideration when discussing the management of CM in PLWH. More invasive interventions should be considered, given the lack of efficacy exhibited by potentially harmful medical treatments traditionally administered in cases of idiopathic ICP such as acetazolamide (47, 48). Furthermore, the overarching goal of additional invasive interventions is to diminish disability and increase the overall quality of life for PLWH who have survived CM infection.

Therapeutic Lumbar Punctures

An association between increased fungal burden at baseline and increased baseline CSF opening pressure (CSFOP) has been established in HIV-associated cryptococcal meningitis, and aggressive management of increased intracranial pressure (IICP) is the current standard to improve morbidity and mortality in CM infection (49, 50). Baseline CSF opening pressure obtained via LP should be rapidly obtained in all patients with confirmed or suspected CM infection unless the patient presents with altered mental status (46). Indications of altered mental status upon presentation would necessitate further investigation via neuroimaging, thus superseding a baseline LP, however, CSFOP measurements should remain a priority in all positive or possible CM cases (46). CSFOP measurements are sensitive to sex, age, and body mass index differences. Still, the current standard range in clinical practice ICP measured by LP in adults in a typical clinical setting should now be regarded as 6 to 25 cmH2O. (51, 52). A general population means of about 18 cmH2O should be considered when studying IICP in the context of HIV-CM concurrent infection (52, 53).

Performing therapeutic LP to drain CSF to achieve CSP closing pressure of less than 20 cmH2O is a treatment option to supplement medication management (46). This intervention can be carried out daily until the desired measurement has been achieved and CSF pressure has normalized, and recent clinical findings have determined a 69% relative survival protection rate due to repeat therapeutic LP (46). While the number of LPs received by patients is highly variable, scheduling two therapeutic LPs during the first week of antifungal treatment is strongly suggested, alongside an additional LP two weeks post-diagnosis, may be instrumental in symptom management and reduction of neurological sequelae (54). The effects of raised ICF can be acute and present within the first two weeks, although results may not be present until week 10 in some individuals. These findings suggest that formulating an updated standardized therapeutic LP schedule, which also considers suboptimal treatment environments, would improve patient outcomes (54). The implementation of a standardized LP treatment plan for patients who meet the criteria would address this specific treatment goal and would support effective long-term management (54).

Ventriculostomy and Ventriculoperitoneal Shunt

Performance of a ventriculostomy, temporary placement of a catheter to divert CSF build-up to an external collection system, or surgical placement of a ventriculoperitoneal shunt (VPS) are two additional invasive strategies utilized for acute and long-term management of increased ICP in CM patients (47, 55). VPS placement averts CSF build-up from the lateral ventricles to the peritoneum via a pressure valve (56). Historically, the increased risk of infection in HIV-positive individuals with CM has dissuaded surgeons from ventriculostomy and VPS placement, but recent investigations, including retrospective cohort studies, have sought to determine the long-term benefits of VPS in ICP management despite the assumed increased risk of infection. VSP placement is applicable as a secondary treatment for patients who have had a significant amount of CSF removed via LP but need sustained intervention to remain neurologically asymptomatic without interfering with antifungal treatment (57, 59).

Although surgical complications can pose a threat to an individual with HIV-CM, various studies have succeeded in delineating a relationship between the use of VPS and improved survival rates (47, 57, 60, 61). Such studies have demonstrated that surgical infection due to VPS placement is uncommon and generally should not be a significant factor dissuading clinicians from neurosurgical intervention in this context (47, 57, 60, 61). Additionally, a related study performed in rural Central Africa examined the safety of LP in resource-limited settings, and determined that when a LP is performed in accordance with local clinical standards, the procedure only resulted in moderate, non-life threatening, adverse events (62). Incidence and mortality remain significant issues with HIV-CM concurrent infection; nevertheless, it has been demonstrated that in under-resourced circumstances, particularly in the absence of neuroimaging, LPs are not solely significant contributors in CM diagnosis, but also can provide a safe route of intervention (62). Increased utilization of the invasive interventions discussed can potentially improve overall outcomes, especially in cases of substantially increased CSFOP, while accounting for patient age and the severity of fungal infection (61).

Conclusion

Cryptococcal meningitis continues to be the most common form of meningitis in HIV-positive adult individuals globally and the most impactful fungal infection affecting HIV-positive individuals. This is due to the damaging and potentially lifelong neurological and neurocognitive effects that can affect the CNS through lesions, hydrocephalus, increased cranial pressure, and more, along with visual and auditory complications against already susceptible people. Newer point-of-care methods like cryptococcal antigen lateral flow assays are being explored outside of ART. These methods are faster and easier to administer, which can help to combat the high mortality rate of the disease. This will be particularly true in areas with limited resources like sub-Saharan Africa and Southeast Asia, where CM remains at an all-time high, so the screening and diagnostic processes can be lessened to reach the treatment phase more rapidly.

Increased intracranial pressure remains a problem in CM that, in many cases, needs to be addressed with more intrusive strategies to help improve patients' overall quality of life. These include therapeutic LPs, ventriculostomies, and ventriculoperitoneal shunt placement that work to relieve the intracranial pressure and possibly diminish the risk of long-term sequelae associated with excess CSP and IICP. However, the need to establish the longevity of the functionality of these interventions remains and there is a substantial need to further explore to understand potential complications, especially among HIV-positive individuals of all ages. Along with the limitation of research on performing a ventriculostomy and ventriculoperitoneal shunts, further research is needed on the acute and long-term effects of CM on HIV-positive pediatric populations because only a handful of findings are available and current surrounding the potential consequences and complications faced by this age group.

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