ORIGINAL ARTICLE

Stroke Incidence in Cerebral Aspergillosis: A meta-analysis

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ABSTRACT

Cerebral aspergillosis is an opportunistic disease most commonly caused by the fungus Aspergillus fumigatus. Invasive infection with Aspergillus has been reported due to the extension of infection usually affecting immune-compromised individuals. The fungus may cause direct artery invasion or mycotic aneurysm, causing intracerebral or subarachnoid hemorrhage. The study compiled data from 27 studies with a combined sample size of 82 individuals. The results showed that these patients had a high risk of stroke. The risk was higher in immunocompromised patients with lung or kidney transplantation and debilitated patients who have alcoholism, diabetes mellitus, liver failure, renal failure, drug addiction, leukemia, or malignant lymphoma. Radiographic studies of these patients showed narrowed cerebral vessels. This meta-analysis investigates the incidence rate of stroke in patients with cerebral aspergillosis, its presenting signs, and a review of risk factors and complications of aspergillosis. Advanced diagnostic and treatment approaches to cerebral aspergillosis and future research directions are discussed.

INTRODUCTION

Cerebral aspergillosis is an opportunistic disease most commonly caused by the fungus Aspergillus fumigatus. Invasive infection with Aspergillus has been reported due to extension of infection from paranasal sinuses, during a contaminated intrathecal antibiotic administration, or after a transsphenoidal surgery as a postoperative complication [1]. However, this rare disease usually affects immune-compromised individuals and debilitated patients suffering from alcoholism, diabetes mellitus, liver failure, renal failure, drug addiction, leukemia, or malignant lymphoma. Aspergillus species are known to be

angioinvasive, increasing the risk for occlusive thrombosis, embolism, and infarction. During infection of the Central nervous system (CNS), the fungus tends to perforate arteries, leading to infarction of brain parenchyma [2]. The neurological manifestations of the disease include stroke and cases of extended infection cerebritis, meningitis, cranial sinus thrombosis, ventriculitis, and abscess formation [3]. Hence, patients show various clinical signs and symptoms, such as fever, headache, visual disturbances, seizures, gait abnormalities, weakness, confusion, cognitive defects, and focal neurological findings [4]. Cerebral aspergillosis has an extremely poor prognosis once neurological signs of the disease begin to manifest themselves; the average recorded survival rate is not more than five to nine days [5].

A stroke occurs when the blood supply to the brain is interrupted or there is sudden bleeding in the brain. Fungal infections rarely cause stroke, but the most common pathogens to do so among the fungi are Candida and Aspergillus species. The fungus usually causes intracerebral or subarachnoid hemorrhage. This may occur due to direct artery invasion or rupture of mycotic aneurysm. Hyphae of Aspergillus fumigatus invade the vessel wall, which is already damaged due to the invasion of neutrophils and necrosis [6]. This triggers intraluminal thrombus formation, leading to hemorrhagic infarction, the usual cause of stroke in these patients [7].

Risk Factors

Aspergillosis affects both genders equally and causes infection in people of any age. The fungus is a part of the normal environment flora and rarely causes disease in healthy individuals. Therefore, aspergillosis is mainly a disease of immunocompromised individuals, and its invasive form typically occurs in immunosuppressed individuals. The most significant group among the immunosuppressed individuals are the organ transplant recipients, especially renal transplant recipients. Risk factors influencing disease are the level of immunosuppression, type of organ transplant, and extent of current and previous exposure to Aspergillus [8].

However, people with advanced acquired immunodeficiency syndrome (AIDS), hematological malignancies, liver failure, solid tumors, intravenous drug abuse, poorly managed diabetes mellitus, and chronic granulomatous diseases also risk developing aspergillosis [1].

Certain medications also increase a patient's vulnerability to this fungal infection. With the advent of medical interventions capable of impairing the host's immune system, such as steroids, immunosuppressive agents, and broad-spectrum antibiotics, the incidence of cerebral and invasive aspergillosis has increased.

Incidence Rate

The rate of cerebral aspergillosis among patients with invasive aspergillosis has been reported to be 10-15%. [i]Since the fungus is angioinvasive in nature, stroke can be manifested as hemorrhagic infarcts or as one of the presenting symptoms of disseminated aspergillosis [9]

Authors	Year	Title	No. of patients	Outcome: Was the stroke reported?
A P Boon, D H Adams	1990	Cerebral Aspergillosis in liver transplantation	9	stroke was documented in 7 out of 9 patients (their brains showed gross haemorrhagic infarcts)
Carrie M. Hersh, DO, MS, Seby, John, MD, Adnan Subei, DO, Mary A. Willis, MD, Gregory S. Kosmorsky, DO, Richard A. Prayson, MD, MEd, Adarsh Bhimraj, MD	2016	Optic Neuropathy and Stroke Secondary to Invasive Aspergillus in an Immunocompetent Patient	1	yes
Carrazana, E. J. Rossitch, E., Jr. Morris, J.	1991	Isolated central nervous system aspergillosis in the acquired immunodeficiency syndrome	1	No
Chen Lin, George A. Barrio, Lynne M. Hurwitz, Peter G. Kranz	2014	Cerebral Air Embolism from Angioinvasive Cavitary Aspergillosis	1	yes
Goyal, N. Narula, H. Chaturvedi, J. Agrawal, S. Dash, C. Meena, S. Kaistha, N.	2020	Angio-invasive Cerebral Aspergillosis Resulting in Hemispheric Infarct in an Immunocompetent Man	1	yes
Ho, C. L.Deruytter, M. J.	2004	CNS aspergillosis with mycotic aneurysm, cerebral granuloma, and infarction	1	yes
Iihara, K. Makita, Y. Nabeshima, S. Tei, T. Keyaki, A. Nioka, H.	1990	Aspergillosis of the central nervous system causing subarachnoid haemorrhage from mycotic aneurysm of the basilar artery--case report	1	yes
Kavi, T. Madan, N. Majic, T. Rosengart, A. Maya, M. Bannykh, S. Lahiri, S.	2017	Angioinvasive Aspergillus-associated Stroke in an Immunocompetent Host Following Cardiac Surgery and ECMO	1	yes
Li W, Shafi N, Periakaruppan R, Valyi-Nagy T, Groth J, Testai FD.	2007	Cerebral aspergillosis in a diabetic patient leading to cerebral artery occlusion and ischemic stroke: a case report and literature review.	1	yes
R P Haran 1, M J Chandy	1993	Intracranial aspergillus granuloma	13	1 out 13 cases of intracranial aspergillosis presented with stroke
Martins, H. S. da Silva, T. R. Scalabrini-Neto, A.Velasco, I. T.	2010	Cerebral vasculitis caused by Aspergillus simulating ischemic stroke in an immunocompetent patient	1	yes
Mikhael, M. A. Rushovich, A. M. Ciric, I.	1985	Magnetic resonance imaging of cerebral aspergillosis	1	yes
Mohamed Ibrahim, Norlinah Ngow, Harris Abdullah BB, Hamidon	2007	Angioinvasive cerebral aspergillosis presenting as acute ischaemic stroke in a patient with diabetes mellitus	1	yes
Muraoka, S. Araki, Y. Izumi, T. Takeuchi, K. Okamoto, S. Wakabayashi, T.	2016	Cerebral Infarction and Subarachnoid Haemorrhage Caused by Central Nervous System Aspergillus Infection	1	yes

Nadkarni, T. D. Desai, K. I. Muzumdar, D. Goel, A. Shenoy, A.	2003	Ischaemic complications after surgical resection of intracranial aspergilloma	1	yes
Takeshita, Mikihiko Izawa, Masahiro Kubo, Osami Tanikawa, Tatsuya Onda, Hideaki Wanifuchi, Hiroshi Tamura, Yukie Kagawa, Mizuo	1992	Aspergillotic aneurysm formation of cerebral artery following neurosurgical operation	1	aspergillotic aneurysm leading to subarachnoid haemorrhage
Tan, R. M. R. Ganau, M. Jeelani, N. U. O. Tahir, Z. Mankad, K. Kachramanoglou, C. Prabhakar, P. Goulden, N. Samarasinghe, S.	2017	Central nervous system aspergillosis resembling haemorrhagic brain infarct in a paediatric leukaemia patient	1	yes
Vijayvargiya, P Javed, I Moreno, J Mynt, MA Kotapka, M Zaki, R Ortiz, J	2013	Pituitary aspergillosis in a kidney transplant recipient and review of the literature	1	yes
Walsh, T. J. Hier, D. B. Caplan, L. R.	1985	Aspergillosis of the central nervous system: clinicopathological analysis of 17 patients	17	11 out of 17 autopsied patients had haemorrhagic infarction
João Batista Alves Segundo, Marcos Antonio Custódio Neto da Silva, Walbert Edson Muniz Filho, Anna Cyntia Brandão Nascimento, Flávia Castello Branco Vidal, Geusa Felipa de Barros Bezerra, Graça Maria de Castro Viana, Maria do Desterro Soares Brandão Nascimento	2014	Cerebral aspergillosis in a patient with leprosy and diabetes: a case report	1	yes
Carla Anciones *, Alicia de Felipe *, Asier de Albóniga-Chindurza *, Fernado Acebrón *, Hector Pián †, Jaime Masjuán *, Iñigo Corral *	2018	Acute Stroke as First Manifestation of Cerebral Aspergillosis	9	5 out 9 had stroke as first symptom
Gupta, Juhi Chakrabarty, Biswaroop Singh, Gagandeep Singh, Sonali Kumar, Atin Xess, Immaculata Jauhari, Prashant Gulati, Sheffali	2021	A rare infective cause of stroke in an immunocompetent child	1	yes
Lau, Alan H.C. Takeshita, Moiriyuki Ishii, Nobuyoshi	1991	Mycotic (Aspergillus) Arteritis Resulting in Fatal Subarachnoid Hemorrhage: A Case Report	1	yes
Jitender Saini 1, Arun Kumar Gupta, Milan Babulal Jolapara, Somenath Chatterjee, Hima S Pendharkar, Chandrasekharan Kesavadas, Vishnupuri Venkatraman Radhakrishnan	2010	Imaging findings in intracranial aspergillus infection in immunocompetent patients	12	Imaging of 3 out of 12 patients showed infarction
Guermazi, A.	2002	Cerebral and spinal cord involvement resulting from invasive aspergillosis	1	yes
Vergara, G. E. Roura, N. Del Castillo, M. Mora, A. Alcorta, S. C. Mormandi, R. Cervio, A. Salvat, J.	2015	Cervical aspergillosis with dissemination to the central nervous system: Case reports and review of the literature]	1	yes

Table 1. Summary of the studies included in the meta-analysis.

RESULTS

Boon et al. reported nine cases identified with cerebral aspergillosis out of forty-four that underwent liver transplantation. In the autopsy reports, seven of nine brains had gross hemorrhagic infarctions [10]. In another study, thirteen cases of intracranial aspergillus granuloma were studied retrospectively over twelve years. Out of the thirteen patients, one had a stroke-like syndrome on presentation. Imaging studies of twelve invasive aspergillosis patients were studied retrospectively for ten years. Computed Tomography Scan (CT scan) showed infarcts in three patients whose angiography studies indicated narrowed cerebral blood vessels [5].

Anciones et al. reported a retrospective analysis of a clinical series of patients with invasive aspergillosis between 2011 and 2017. Nine patients were diagnosed with invasive aspergillosis. Five patients presented with stroke as the first manifestation and were selected for further analysis [9]. Aspergillosis of the central nervous system was studied by Walsh et al. in seventeen autopsied patients; eleven had a hemorrhagic infarction in their brains [11]. Saini et al. researched imaging findings in intracranial aspergillus infection in thirteen immunocompetent patients. The imaging of three out of twelve patients showed infarction [12].

In our retrospective study, 20 case reports (96%) reported stroke in the clinical presentation of cerebral aspergillosis patients. At the same time, 58% of all patients in these studies had a stroke.

The clinical diagnosis of cerebral aspergillosis is difficult to establish. In most previously reported cases, it was made late in the disease course or at the time of autopsy [10]. However, occasionally, patients presenting with mild headaches and low-grade fever, despite appropriate antibiotic therapy for a known bacterial infection, especially in an immunocompromised patient, should be further investigated for a risk of possible stroke.

While the diagnosis is difficult, a delay in initiating therapy for aspergillosis is fatal. Multiple diagnostic approaches must be taken promptly to confirm if an opportunistic infection is suspected [11]. Examination of cerebrospinal fluid (CSF) in cerebral aspergillosis is variable. CSF findings are usually nondiagnostic, with only a slight increase in protein level, and occasionally lymphocytic pleocytosis is reported. Aspergillus species rarely recovered from spinal fluid cultures. Cerebral abscesses or granulomas have very little or no identifiable meningeal involvement. Isolation of Aspergillus organisms from sites outside the central nervous system might exclude the need for a brain biopsy. In this respect, radiological studies will prove useful by identifying pulmonary infiltrations or paranasal sinus involvement [11]. Early Magnetic resonance imaging (MRI) and/or serial CT scans are the only potentially helpful diagnostic procedures short of surgery.

The MRI is more useful than the CT scan, as it can detect the disease's early "encephalitic" stage before it becomes abnormal. CT scans show nonspecific findings such as enhanced lesions and/or large brain

abscesses. Serial CT scans can be helpful when MRI is unavailable, as fungal lesions are usually distinguished by instant progression, with hemorrhage and enlarging infarction [11].

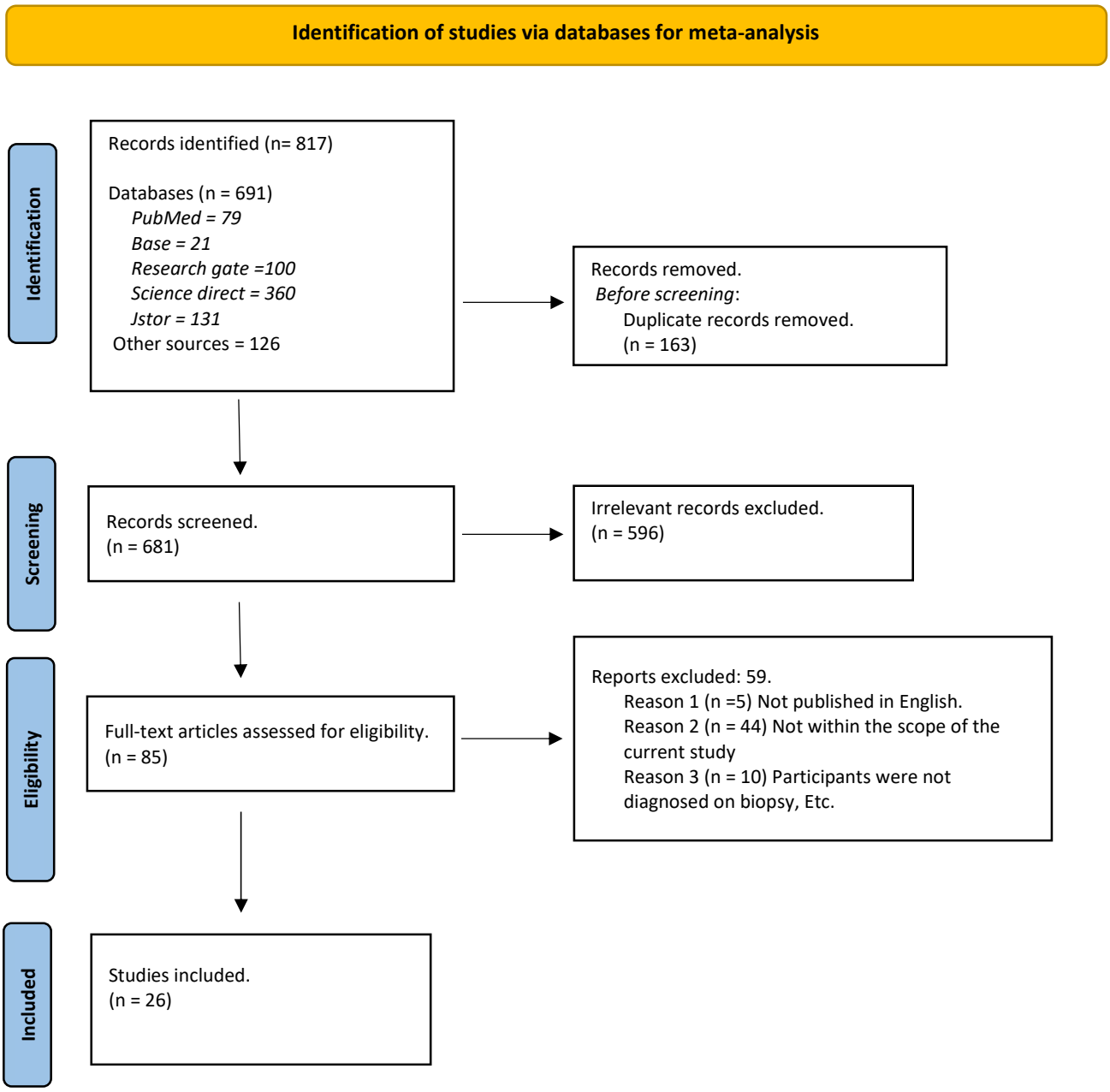

Table 2. PRISMA flow diagram for the study search.

It is difficult to differentiate aspergillus-related mass lesions from other lesions, even with MRI. However, in previously reported cases, MR images distinctly revealed the lesion's encasement of the left internal carotid artery, which proved useful for determining the therapeutic strategies and predicting the prognosis

[6]. Brain MRI shows highly viscous and cellular species of Aspergillus and associated infarcted tissue as restricted diffusion. When present, ring enhancement can correspond with capsule formation from chronic inflammation and the production of granulation tissue [11]. Intermediate-signal lesions on MRI scans with surrounding high-signal edema should raise the question of fungal infection. Brain destruction and surrounding reactive edema favor fungal infection in the appropriate clinical settings [15].

Recently, 0.15-T MR findings for Aspergillus granuloma have been reported. Using a 1.5-T MR scanner, the lesion was found to be iso signal intensity on a T1-weighted image and high signal intensity on a T2-weighted image. A confirmed diagnosis of this rare disease can only be obtained by biopsy and culture of the resected specimen [6].

Recently, fungal antigens, including Galactomannan (GM), proved helpful in diagnosing cerebral aspergillosis. The sensitivity and specificity of serial GM monitoring are 92.6% and 95.4%, respectively, as reported by Maertens et al. Other investigators also reported a high sensitivity of 67% to 100% and specificity of 81% to 100%. The detection of GM at an early stage of disease and the quantitative titers produced by the sandwich Enzyme-linked immunosorbent assay (ELISA) offers new approaches to managing Invasive aspergillosis [2]. ELISA of the CSF has a lower specificity and slightly higher sensitivity [16].

Polymerase chain reaction (PCR) assays have also been shown to be another promising diagnostic setting; however, they have not been part of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Disease Mycoses Study Group (EORTC/MSG) Invasive Fungal Infection (IFI) consensus criteria yet because there are a variety of methods but a lack of standardization [11].

TREATMENT

At present, the treatment of cerebral aspergillosis is very unsatisfactory. Two key steps to an improved prognosis in patients with CNS Aspergillosis exist. The first is early recognition and antifungal therapy for the infection. The second is prompt surgical intervention with endovascular surgery to treat aneurysmal formation in major arteries [17].

Radical resection and combined chemotherapy with amphotericin-B, Fluorouracil (5-FC), and rifampicin are available. However, Amphotericin B has serious side effects, so its administration should be discontinued in many cases. A case has been reported in which treatment with amphotericin-B and rifampicin failed to give satisfactory results but succeeded when the medication was changed from rifampicin to 5-FC, highlighting the importance of the in-vitro sensitivity test. In this case, the progress in diminution of the right eye vision was arrested to some extent by postoperative administration of

amphotericin-B and 5-FC. However, the administration had to be discontinued because of myocarditis and the subsequent deterioration in the patient's general condition. Despite recent improvements in diagnosis and the advent of Caspofungin and newer formulations of amphotericin B, the mortality rate of Cerebral aspergillosis is still 100% [11].

The effectiveness of different antifungals, each with different recommendations, has been compared in many studies. Previously, amphotericin B (AmB) was believed to be the drug of choice for Aspergillosis; however, recent studies have shown that voriconazole has better efficacy and may provide better safety and survival. A randomized controlled trial of 391 patients observed that, at 12 weeks, the survival percentage of patients with aspergillosis was 70.8% in the voriconazole group and 57.9% in the Amphotericin B group. Some consideration has occurred about the superiority of voriconazole over Amphotericin B, but the Infectious Disease Society of America guidelines recommend voriconazole for Cerebral aspergillosis. Voriconazole is believed to be superior to other antifungal therapies for CNS aspergillosis because of its ability to penetrate the blood-brain barrier. The adverse side effects of both treatments should be kept in mind while administering. A notable concern in any transplant recipient is renal damage/failure, which is a common adverse side effect of Amphotericin B. Thus, voriconazole has not only proven to be effective in treating invasive Aspergillosis, but it may also be more effective in patients with renal failure than the previous gold standard– Amphotericin B [8].

DISCUSSION

Cerebral aspergillosis is a fatal disease. Aspergillus species are everywhere in nature, and inhalation of infectious conidia is frequent. Tissue invasion and clinical infection resulting from aspergillus in immunocompetent individuals is uncommon. However, In the setting of immunosuppression associated with therapy for hematologic malignancies, hematopoietic cell transplantation, or solid organ transplantation, the risk for infection is more considerable [11].

It is well known that Aspergillus causes vasculitis. According to Ihara K. et al., vasculitis can follow three courses: 1) thrombus formation, causing hemorrhagic infarction and brain abscess; 2) sudden massive hemorrhage; and 3) formation of an aneurysm. Fungal aneurysms tend to be different from bacterial aneurysms in that they are often found at the base of the brain, in major vessels, and their developmental mechanism is more often by direct invasion from the luminal surface and the adventitia than by involvement of the vasa vasorum. In many reported cases, ruptured vessels were located at the base of the brain, involving the internal carotid artery, basilar artery, anterior cerebral, middle cerebral, posterior cerebral, posterior communicating, and vertebral arteries. Many cases developed massive Subarachnoid hemorrhage accompanied by intraventricular hemorrhage, and all the patients died [6].

In another case, a patient with CNS aspergillosis presented with worsening motor deficits, and an MRI study was done, which showed a fungiform lesion suggestive of vasculitis, with pyriform areas of increased signal intensity, hemorrhagic foci and diffuse meningeal enhancement with contrast. The patient was initially treated with the administration of liposomal amphotericin B. However, she progressed with progressive symptoms worsening when intravenous Caspofungin was started. Despite all efforts, the patient died shortly with mesenteric arterial vasculitis [18].

In a study by Vijayvargiya et al., a patient with a kidney transplant, a year after the episode of transplant rejection, was diagnosed with a pituitary adenoma. Four months later, the patient was emergently admitted for left monocular temporal hemianopia with ocular ptosis concerning optic chiasm and third cranial nerve compression along the ipsilateral cavernous sinus. 72 hours later, her mental status significantly declined, requiring re-intubation, with a Glasgow coma scale (GCS) of 4/15. CT scan was obtained, which showed an extensive left anterior cerebral artery ischemic stroke. The patient soon died afterward [8].

Disseminated aspergillosis mainly involves CNS, but localized involvement in the spinal cord is rarely seen. Compression of the spinal cord resulting from aspergillus epidural abscess with or without vertebral destruction is unusual. Furthermore, localized involvement of the spinal cord is extremely rare. Most cases reported have occurred after direct extension into the spinal canal from the lung or disc space infection. When the infection involves the spinal cord and extends into the spinal cord substance, demyelinating changes are observed [8].

Another case reported by Lin Chen et al. was cerebral infarction from an air embolus originating from an angioinvasive pulmonary aspergillosis. Vascular invasion following infarction and tissue necrosis is one hallmark of pulmonary aspergillus infection. Once cavitary lesions are formed in the lungs, they can produce air or be a conduit for air-filled lung tissue and, along with a pressure gradient, can either enter the vascular system directly or indirectly through a venoarterial right to left shunt, with final growth into the cerebral vasculature [19].

CONCLUSION

Cerebral aspergillosis is an opportunistic invasive infection that usually affects immunocompromised individuals. Patients may experience direct arterial invasion or mycotic aneurysms, leading to intracerebral and subarachnoid disease. Our study found that these patients were at increased risk of stroke. The risk of stroke is higher in immunocompromised lung or kidney transplant patients and in patients with other comorbidities. Careful evaluation of these patients is strongly recommended to minimize the risk of acute stroke. Complementing neurophysiological studies with imaging techniques may aid in accurate and early diagnosis and future research.

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