**Surgical and Non-surgical Survival Among Cerebral Aspergillosis: Outcome Comparison and Review of the Literature**

***Introduction***

Fungal infections of the brain are often associated with immunocompromised patients and carry high rates of morbidity and mortality. They have various nonspecific presentations, diagnosis is difficult and invasive, and they require pathogen-specific antifungal treatment. Central nervous system (CNS) fungal infections are acquired through inhalation, inoculation, trauma, and surgery, usually ENT or Neurosurgery. Rapid diagnosis and treatment are associated with more favorable outcomes.1 In most cases, imaging resembles other pathology and a tissue sample is required for a definite diagnosis.2 The treatment options available for systematic fungal infection may differ from CNS infection due to the drugs’ abilities to cross the blood brain barrier (BBB). Antifungals such as voriconazole, fluconazole and flucytosine have shown CNS penetration, therefore they are good candidates for brain fungal infections.3 Studies have shown neurosurgical intervention for CNS fungal infections is associated with improved outcomes.4

Aspergillus is an aggressive fungus that occurs in spite of prophylaxis.5 Cerebral aspergillosis is one of the most fatal infections with mortality rates of approximately 99% before the introduction of voriconazole.6 The presenting symptoms include headache, fever, irritability, proptosis, focal deficits progressive weakness and altered mental status.7,8, 9, 10 In some cases, an acute stroke can be the first presenting sign.5 In cerebral aspergillosis patients that present with acute stroke symptoms, the administration of tPA can cause hemorrhage due to vasculitis.5 Diabetic and immunocompromised patients are high risk groups for the development of aspergillosis.5, 10

Imaging shows an array of findings in the frontal and temporal lobes, the basal ganglia, thalamus and corpus callosum.5, 11, 12 An infarction in the corpus callosum is particularly suggestive of cerebral aspergillosis.13 Aspergillomas can be mistaken as a tumor, hemorrhage, or abscess, and Rhino-cerebral Aspergillosis findings involve hyperdense sinuses.7, 11 Specific magnetic resonance imaging (MRI) findings include ring enhancing lesions with vasogenic edema.8, 14, 15 Diffusion weighted imaging (DWI) shows hyperintensity, and apparent diffusion coefficient (ADC) shows hypointensity suggestive of restricted diffusion. A definite diagnosis of aspergillosis requires a positive culture from brain tissue or CSF. If a positive culture cannot be obtained, a histological or cytological evidence from a CNS specimen and growth of aspergillus from sterile site or bronchoalveolar lavage can lead to a definitive diagnosis as well.16

The emergence of voriconazole has increased survival rates of cerebral aspergillosis form 0-1% to 31%.6, 16 Voriconazole is most effective when used as the primary antifungal rather than salvage therapy after other antimicrobials fail.4 Voriconazole may be discontinued once all lesions have resolve and any underlying conditions have been reversed.17

Neurosurgery has been shown to play a critical role in the identification and treatment of Aspergillosis.7  The combination of voriconazole and surgical resection or aspiration shows better response and survival over any other therapy, with Schwartz et al reporting the relative risk of 2.1.4, 6, 15 Surgical resection or aspiration have been shown improve survival due to enhanced drug penetration.6, 10, 18

With the diagnosis of CNS fungal infections on the rise,2 necessity for a guide regarding the course of the treatment is needed. In this paper we aim to primarily compare outcomes in patients with cerebral aspergillosis who underwent neurosurgical intervention compared to those who did not. Furthermore, we sought to compare outcomes of patients based on age, antifungal agents used, the number of antifungals used cumulatively. We reviewed the reported data and provide a systemic analysis of the available information.

***Methods***

Search selection

Using PubMed, a search was conducted in March 2019 by study’s Author (HBP) using keyword “cerebral aspergillosis”. No restrictions were placed on language, publication type, or publication date. Articles were excluded if their title contained a fungus that was not Aspergillus, the patient had two or more concurrent fungal infections, or the patient had non-fungal cause of infection. Following a concise examination of each article, it was determined by the author if it contained pertinent diagnostic or treatment information to be considered a valuable source in this article. A detailed description of the strategy and selection criteria is provided in Supplemental Table 1.

Data Extraction

For chosen articles, we recorded the age of patients, neurosurgical involvement and their specific intervention, the antifungals administered and whether or not intrathecal antifungals were administered. We also recorded the classification of the articles we reviewed.

***Results***

**Search Results**

We followed the guidelines of PRISMA in the writing of this paper. The search resulted a total of 1,169 articles of which 324 met the eligibility criteria, were reviewed in full and used for data collection. A total of 199 studies including 248 patients were included in the analysis. Most studies included in the analysis were case reports and retrospective reviews. The extracted clinical data is presented in tables 1.

**Overall morbidity and mortality associated with aspergillosis infections**

Of the 248 patients included in this study, 98 died during the duration of their respective studies. Eighteen of those patients expired due to other causes, and 80 expired due to aspergillosis. Overall mortality of patients attributable to aspergillosis in this review was slightly over 32%. (This is consistent with what the literature shows in introduction)

**Morbidity and mortality with and without surgery**

Surgical intervention was utilized in 189 patients to aid in diagnosis or treatment. Surgical intervention for treatment was used in 102 patients of which 19 were partial resections, 36 were complete resections, and in the remaining 47 cases the extent of the resection was not specified (Table 1). A bivariate analysis of patients expiring from aspergillosis after undergoing surgical resection (Table 1) showed a statistically significant (p <.05) increase in survival for patients undergoing surgery (77.5%) than those who did not (61.0%).

**Morbidity and mortality associated with use of various antifungal agents**

Systemic antifungals were utilized in the treatment of 243 patients. The specific antifungals used in this review are listed in Table 1. Patients surviving aspergillosis received a slightly higher number of anti-fungal agents (M = 2.3, SD = 1.2) than those expiring (M = 1.9, SD = 1.0) though this did not reach statistical significance. A bivariate analysis of patients surviving and expiring from aspergillosis following systemic antifungals (Table 1) showed a statistically significant increased survival for patients who were treated with voriconazole (78.3%; p <.001), itraconazole (82.8%; p <.05), and fluconazole (50%; p <.05). Amphotericin B (61.1%) had borderline significance (p =.05), therefore, it was included in further analysis.

**Linear regression results**

Surgical intervention and utilization of systemic fungal agents were investigated in relationship to expiration to identify potential predictors of decreased expiration after treatment for CNS fungal infection. In univariate analysis (Table 2), patients who underwent surgery or received systemic voriconazole or itraconazole were significantly less likely to expire from their infection. There was a 55% reduction in odds of expiration for those treated with surgery (OR = .45, 95% CI 0.25-0.80, p <0.01).The odds of expiration after treatment with systemic voriconazole and itraconazole were reduced by 68% and 64% respectively (OR =0.32,95% CI 0.18-0.55, p = <0.001; OR=0.36, 95% CI 0.16-0.72, p <0.01.. On univariable analysis, fluconazole with associated with a increased odds of expiration (OR = 2.31, 95% CI 1.01 – 5.30, p<.05) though this was not significant on multivariable analysis (OR = 1.33, 95% CI 0.44-4.06, p = .62).

In multivariable analysis (Table 2), the odds of expiration with surgery were independently reduced by 60% (OR = 0.40,95%CI 0.21-0.75, p < 0.01). The odds of expiration after receiving voriconazole and itraconazole were independently reduced by 86% and 85%, respectively (OR = 0.14, 95% CI 0.05-0.36, p < 0.001; OR = 0.15, 95% CI 0.05-0.38, p <0.001.

***Discussion***

Study Limitations

The present article has expected limitations as the sourced information for the systematic review was from case reports or small case series. A substantial amount of information was missing from various studies including lab values, dosing and mode of delivery for antifungals and timing of the regimen. Further limitations include variation in treatment, unknown health status and comorbidities of patients. Systemic reviews, case reports, and retrospective studies are limited in the data they could collect as they can only report the information the care provider included in patient’s chart, causing limits on what they could analyze and report. The studies included on this paper span a wide period of time. The change in diagnostic modalities and treatments have tremendously changed since the treatment of older papers.

***References***

1. Góralska, Katarzyna, Blaszkowska, Joanna, and Dzikowiec, Magdalena. “Neuroinfections Caused by Fungi.” Infection 46.4 (2018): 443–459. Web.
2. Murthy JMK, Sundaram C. Fungal infections of the central nervous system. In. Biller J, Ferro JM, (eds). Handbook of clinical neurology. Elsevier, New York, 2014; 1383–401.
3. Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. Clin Microbiol Rev. 2014;27:68–88.
4. Schwartz S, Reisman A, Troke PF. The efficacy of voriconazole in the treatment of 192 fungal central nervous system infections: a retrospective analysis. Infection. 2011;39:201–210
5. Anciones, Carla et al. “Acute Stroke as First Manifestation of Cerebral Aspergillosis.” Journal of Stroke and Cerebrovascular Diseases 27.11 (2018): 3289–3293. Web.
6. Schwartz S, Ruhnke M, Ribaud P et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. Blood 2005; 106: 2641–5.
7. Tripathi, Manjul, and Mohindra, Sandeep. “Rhinocerebral Aspergillosis.” The Lancet 392.10150 (2018): e8–e8. Web.
8. Pavlina, Andrew A. et al. “Aspergillus Mural Endocarditis Presenting with Multiple Cerebral Abscesses.” Journal of Cardiothoracic Surgery 13.1 (2018): 1–4. Web.
9. Palacios, Enrique et al. “Magnetic Resonance Imaging in Fungal Infections of the Brain.” Topics in Magnetic Resonance Imaging 23.3 (2014): 199–212. Web.
10. Kourkoumpetis TK, Desalermos A, Muhammed M, et al. Central nervous system aspergillosis: a series of 14 cases from a general hospital and review of 123 cases from the literature. Medicine. 2012;91:328–336.
11. Alahmari, Abdulwahab F. “Medical Treatment of Brain Aspergilloma Followed by MRI: A Case Report.” Radiology Case Reports 14.1 (2019): 103–111. Web.
12. Scully, P, Eileen, Baden, R, Lindsey, and Katz, T, Joel. “Fungal Brain Infections.” Current Opinion in Neurology 21.3 (2008): 347–352. Web.
13. DeLone DR, Goldstein RA, Petermann G, Salamat MS, Miles JM, Knechtle SJ, et al. Disseminated aspergillosis involving the brain: distribution and imaging characteristics. AJNR Am J Neuroradiol. 1999;20(9):1597–604.
14. Keyik B, Edgüer T, Hekimoğlu B. Conventional and diffusion-weighted MR imaging of cerebral aspergillosis. Diagn Interv Radiol. 2005; 11:199–201.
15. Azarpira, Negar, Yazdanpanah, Shahrzad, and Safarian, Arash. “Invasive Fungal Granuloma of the Brain in an Immunocompetent Patient.” Neurosurgery Quarterly 25.1 (2015): 121–123. Web.
16. Schwartz, Stefan et al. “Poor Efficacy of Amphotericin B‐based Therapy in CNS Aspergillosis.” Mycoses 50.3 (2007): 196–200. Web.
17. Stevens DA, Kan VL, Judson MA, et al. Practice guidelines for diseases caused by Aspergillus. Clin Infect Dis. 2000;30:696-709.
18. Thurlbeck WM, Chung A. Other Diffuse Lung Diseases. Chapter 21. In: Thurlbeck WM, Chung A, eds. Pathology of the Lung. New York, NY: Thieme; 2005:601–673.