Infant Central Nervous System Aspergillosis with First-episode of Intracranial Hemorrhage

A case report

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Abstract

**Rationale:** Central nervous system (CNS) aspergillosis has the characteristics of multifocality, polymorphism, and coexistence of pathological types, and missed diagnosis and misdiagnosis frequently occur at the initial stage. The thesis reports a rare case of infant infection of CNS aspergillosis with the first-episode of intracranial hemorrhage.

**Patient concerns:** An 11-month-old female infant suffered convulsion and coma two days after the onset of fever and emesis. Its cranial computed tomography (CT) displayed subdural hemorrhage in the left tentorium cerebelli and tests indicated normal cerebrospinal fluid (CSF). Three days after being hospitalized, the infant had difficulty breathing and its CT presents consolidation in the right lung. However, treatment with ceftriaxone (ivgtt) had no effect on the baby.

**Diagnosis:** The patient’s bronchoalveolar lavage fluid (BALF) was cultured into Aspergillus spp., its galactomannan (GM) antigen in CSF counted 3.0, higher than that in BALF which counted 2.6, and cranial magnetic resonance imaging (MRI) revealed multiple ring reinforced tubercles in sulci. Hence it was clinically diagnosed with CNS aspergillosis.

**Interventions:** Voriconazole for intravenous injection. After the intravenous injection, its trough concentration was 4.2 μg/mL., and it was within the recommended range.

**Outcomes:** After one week’s treatment with voriconazole, the infant’s consciousness was improved. Four weeks later, with normothermia and clear consciousness, the patient was discharged. With oral administration of voriconazole up to 16 weeks, its physical state suggests no relapse and cranial MRI indicated disappearance of nodules in sulci.

**Lessons:** CNS aspergillosis with first-episode of intracranial hemorrhage probably leads to misdiagnosis and GM test combined with cranial MRI can augment its accuracy in the early diagnosis.

**Abbreviations:** BALF = bronchoalveolar lavage fluid, CNS = central nervous system, CSF = cerebrospinal fluid, CT = computed tomography, GM = galactomannan, MRI = magnetic resonance imaging, PCR = polymerase chain reaction.

**Keywords:** aspergillosis, central nervous system, galactomannan, hemorrhage, infant

1. Introduction

Morbidity of central nervous system (CNS) aspergillosis, with high mortality rate and poor prognosis, accounts for 10% to 20% of invasive aspergillosis.\textsuperscript{1,2} Early diagnosis and appropriate treatment could significantly enhance the disease’s prognostic performance. In this case, the infant infected with CNS aspergillosis with first-episode of intracranial hemorrhage has a good prognostic performance; thanks to early clinical diagnosis by taking advantage of galactomannan (GM) test and cranial magnetic resonance imaging (MRI) as well as treatment with voriconazole.

2. Case report

An 11-month old female infant from a warm humid rural area with lush growth of trees and grasses suffered convulsion and coma two days after the onset of fever and emesis. Being healthy in the past, the infant was free of craniocerebral trauma and sinusitis and was not treated with glucocorticoid and immunosuppressant before.

On its arrival, mental confusion, increased muscle tension, and positive Babinski reflex were noted in the physical examination and its vital signs included the following: a temperature of 37.7°C, pulse rate of 165/min, respiratory rate of 40/min, and blood pressure of 97/48 mm Hg. Results of laboratory
examinations were as follows: white cell count was 12,800/mm³, neutrophil count 8320/mm³, hemoglobin count 12.2 g/dL, platelet count 10,200/mm³, C-reactive protein level was 33 mg/L (reference value <8 mg/L), blood biochemistry index and blood clotting function were normal, HIV test result was negative, results of antibody tests for neurotropic virus, namely enterovirus, herpes simplex virus, Epstein–Barr virus (EBV), cytomegalovirus (CMV), human herpes virus and Japanese encephalitis virus were negative, blood culture was negative, white cell count in cerebrospinal fluid (CSF) was 8/mm³, the protein, glucose and chloride level in CSF were normal, and CSF culture showed negative. Results of immunological work-up were as follows: T-lymphocyte subsets (CD3, CD4, and CD8) were normal, CD19 and NK lymphocytes were normal, IgG, IgA, IgM, IgE, complement component 3 (C3), and complement component 4 (C4) were normal and cranial computed tomography (CT) indicated left tentorium subdural haemorrhage (Fig. 1).

Prescription of ceftriaxone (50 mg/kg for each dose, ivgtt, q12h) proved little amelioration of the conditions after the patient was hospitalized. Three days after being hospitalized, the infant had dyspnea and its CT indicated consolidation in the right lung. We performed a bronchoscopy on her. Five days later, the infant’s bronchoalveolar lavage fluid (BALF) was cultured into Aspergillus spp and the GM optical density index in the CSF in this case was 3.0 (bio-rad company), higher than that in the BALF. In addition, cranial MRI presented multiple ring reinforced tubercules in sulci. Hence the patient was clinically diagnosed with CNS aspergillosis and voriconazole was administered to it with loading dose of 9 mg/kg for each dose, ivgtt, q12h, and maintenance dose of 8 mg/kg for each dose, ivgtt, q12h.

After five days treatment, serum trough concentration of voriconazole was 4.2 µg/mL and the infant’s consciousness improved after 1 week treatment with intravenous injection of voriconazole. After 4 weeks treatment, the patient’s temperature returned to normal and its consciousness was restored. The GM test presented with optical density in CSF at 0.1 so the infant was discharged. After oral administration of voriconazole (9 mg/kg for each dose, po, q12h) for 16 weeks, we found in the follow-up visits that the patient’s physical state suggests no relapse, and cranial MRI indicated disappearance of nodules in sulci and lateral ventricle free of expansion.

3. Discussion

The most frequent pathological findings of CNS-invasive aspergillosis are hemorrhage, infarctions, and abscesses. The radiographic pattern is dependent on the source of infection with direct extension from the sinuses, eye, or middle ear often causing only a single abscess within the frontal or temporal lobe, and those developing from hematogenous dissemination causing solitary or multiple small abscesses most frequently at the gray–white junction. Vascular invasion may occur and rupture with the development of a hemorrhagic or ischemic stroke, subarachnoid hemorrhage, or empyema formation. The case of an infant, with its first-episode of subdural hemorrhage at cerebral flex and left tentorium cerebella and short-term formation of multiple pulmonary abscesses, was identified with the disease’s features of aspergillus invasion via hematogenous dissemination.

The disease in children, with its nonspecific clinical manifestation, is mainly manifested as edema in the brain tissue at early stage and then develops diffuse central nervous system symptoms. The patient was sent to hospital for fever, convulsion, and coma and subsequently suffered from dyspnea. Its cranial CT displayed intracranial hemorrhage and pulmonary CT suggested consolidation in the right lung. The infant’s BALF was cultured into Aspergillus spp, and results of its GM test in CSF showed positive. There are published reports and reviews on CNS aspergillosis with hemorrhage. However, CNS aspergillosis with first-episode of intracranial hemorrhage is prone to misdiagnosis as the main causes of infant’s intracranial hemorrhage are vascular malformations and coagulation disorders. In our case, the infant infected with CNS aspergillosis with first-episode of intracranial hemorrhage had later presented with consolidation in the right lung and multiple brain abscesses in sulci, and it did not accord with the pathological process of simple intracranial hemorrhage.

Recent experimental research in this field has shown that certain immune receptor deficiencies may predispose to aspergillosis despite what appears to be a normal immune system. Living in a warm and humid environment with lush growth of trees and grasses, the baby can be exposed to fungal spores for a long time. Even malfunction was not identified in the immunological screening; the patient still had the possibility to be attacked by certain rare immunodeficiency disorders. For instance, deficiencies of interleukin (IL)-4 or IL-6 restrain the interaction of mononuclear cells and interferon-gamma (IFN-γ) produced by T helper cells (Th), causing severe infection of aspergillus. However, due to economic hardship, parents of the infant refused to have the infant genetically tested.

According to European Organization for Research and Treatment of Cancer (EORTC), diagnosis of invasive aspergillosis simultaneously requires the host factor, clinical evidence, confirmatory microbiological evidence and/or histopathological evidence. In addition, CSF culture result is often negative since
CNS aspergillosis seldom invades meninges which gives rise to low diagnostic accuracy of the disease. Owing to limited laboratory technology, no PCR was performed in the case so that aspergillus GM test result in CSF would be adopted to diagnose cerebral aspergillosis patients with high risk of being infected aspergillus. During the treatment, monitoring fluctuation in index of GM testing in CSF would help assess reaction to the treatment. The patient’s optical density (OD) of GM antigen testing in CSF was 3.0, higher than that of BALF of 2.6 (the cutoff value is 1.0) which suggested potential infection of CNS aspergillosis. But as known information uncovered that the precise cut-off value of children stays unclear. In this case, although the patient’s BALF culture showed positive and cranial MRI illustrated multiple ring reinforced tubercles in sulci, the case was clinically diagnosed as CNS aspergillosis on account of the negative CSF culture and without detected cerebral histopathological evidence.

Drug’s plasma concentration is crucial to treatment of invasive aspergillosis for children because treatment often fails for underdosage. According to studies results, it is recommendable to get the plasma concentration levels measured after at least 5 days of voriconazole treatment and the recommended range is 2 to 5 μg/mL. The voriconazole trough concentration of the infant was 4.2 μg/mL, measured on the 5th day after therapy, which was within the recommended concentration range. Voriconazole and some anticonvulsants (such as phenytoin, phenobarbital) may interact, leading to insufficient concentration of therapeutic drug. However, in this case, the patient was treated with midazolam and levetiracetam, which would not affect the plasma concentration of voriconazole. Finally, the patient show significant improvement and good prognosis.

4. Conclusion

Multiple clinical manifestations of infant’s CNS aspergillosis cause difficulties in diagnosis and cases with first-episode of intracranial hemorrhage would probably lead to misdiagnosis. And GM test combined with cerebral MRI can augment the accuracy of the diagnosis.

References

[1] Wannasirikul V, Chayakulkeree M. Multiple brain abscesses caused by *Aspergillus fumigatus* in a patient with systemic lupus erythematosus. J Infect Dis Antimicrob Agents 2012;29:17–20.
[2] Almaskari N, Hussain I, Jamaa S, et al. Aspergillus flavus-induced brain abscess in an immunocompetent child: case report. Sultan Qaboos Univ Med J 2016;16:246.
[3] Patterson TF, Denning DW, Fishman JA, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63:e1.
[4] Sun Y, Yu J, Li G, et al. Intracranial aspergillus fumigatus infection complicated with cavernous hemangioma: case report and literature review. Int J Clin Exp Med 2015;8:20524.
[5] Dotis J, Josifidis E, Roilides E. Central nervous system aspergillosis in children: a systematic review of reported cases[J]. Int J Infect Dis 2007;11:381.
[6] McCarthy MW, Kalasauskas D, Petrains V, et al. Fungal infections of the central nervous system in children. J Pediatric Infect Dis Soc 2017;6:123–33.
[7] Ferwerda B, Ferwerda G, Plantinga TS, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med 2009;361:1760–7.
[8] Cenci E, Mencacci A, Casagranda A, et al. Impaired antifungal effector activity but not inflammatory cell recruitment in interleukin-6-deficient mice with invasive pulmonary aspergillosis. J Infect Dis 2001;184:610.
[9] Monneret G, Vener F, Kullberg BJ, et al. ICU-acquired immunosuppression and the risk for secondary fungal infections. Med Mycol 2011;49 (suppl 1):S17–23.
[10] De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46:1813–21.
[11] Buchheidt D, Reinwald M, Spiess B, et al. Biomarker-based diagnostic work-up of invasive pulmonary aspergillosis in immunocompromised paediatric patients—is aspergillus PCR appropriate? Mycoses 2016;59:67–74.
[12] Viscoli C, Machetti M, Gazzola P, et al. Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. J Clin Microbiol 2002;40:1496.
[13] Verweij PE, Brinkman K, Kremer HP, et al. Aspergillus meningitis: diagnosis by non-culture-based microbiological methods and management. J Clin Microbiol 1999;37:1186–9.
[14] Trifilio S, Pennick G, Pi J, et al. Monitoring plasma voriconazole levels may be necessary to avoid subtherapeutic levels in hematopoietic stem cell transplant recipients. Cancer 2007;109:1532–5.