

Screening of the central nervous system in children with invasive pulmonary aspergillosis



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ABSTRACT

The existing guidelines regarding the management of invasive pulmonary aspergillosis do not recommend screening of the extra-pulmonary sites. Due to the fact that the presence of central nervous system (CNS) aspergillosis will influence treatment decisions regarding which antifungal to use and the aimed target concentrations of azoles in plasma, to be informed about dissemination of the infection to the CNS is absolutely necessary. We demonstrate the need for a structured approach to screening of pediatric patients for CNS aspergillosis.

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1. Introduction

Children with hematological malignancies are at high risk for developing invasive pulmonary aspergillosis (IPA) with a high mortality rate [1–3], despite their currently good prognosis of the underlying malignancy. The most frequent extra-pulmonary site in children is the central nervous system (CNS) [4]. Central nervous system involvement is reported in a frequency of 9–39% with exceeding mortality rates of 88% and higher [3,4]. Voriconazole is the mainstay of systemic treatment for cerebral aspergillosis due to its good penetration into the central nervous system. This drug has substantially reduced the mortality rate to 65% [5].

To our knowledge, the existing guidelines regarding the management of persistent febrile neutropenia or invasive aspergillosis [6–8] do not recommend screening of the extra-pulmonary sites in the absence of localized signs and symptoms and/or in those situations where a proven or probable IPA [9] has been diagnosed.

Due to the fact that the presence of CNS aspergillosis will influence treatment decisions regarding which antifungal to use and the aimed target concentrations of azoles in plasma, to be informed about dissemination of the infection to the CNS is absolutely necessary. We demonstrate the need for a structured approach to screening of pediatric patients for CNS aspergillosis by using two clinical cases to exemplify this. Next we discuss the possible indications when to perform this diagnostic work-up.

2. Case

2.1. Case 1

An 8-year-old boy presented with an episode of febrile neutropenia during his treatment for High Risk Acute Lymphoblastic Leukemia (HR-ALL). Broad spectrum antibiotics were started and galactomannan (GM) screening was performed according to our local protocols (e.g., twice weekly during neutropenia irrespective of fever). Galactomannan in serum showed an index of 0.6 (negative < 0.5) and suspicion of invasive aspergillosis was risen. Treatment with voriconazole (8 mg/kg/day including loading dose of 12 mg/kg/day) i.v. was started (day 0) and further diagnostic

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work-up was performed. Culture of the sputum was positive for *Aspergillus fumigatus*. HRCT-thorax revealed five round densities and a cavity forming lesion resembling an air crescent sign, suggestive of invasive pulmonary aspergillosis. Voriconazole treatment was switched (day +4) to oral formulation (200 mg twice a day) due to a satisfactory clinical condition and he was discharged on day 5. Two weeks after the boy was discharged from the hospital he presented with fatigue, headache and vomiting (day +19). CT-cerebrum showed two large abscesses causing midline shift (Fig. 1). CNS aspergillosis was suspected and surgical drainage of one abscess was performed. Direct microscopy of the fluid revealed branching hyphae compatible with *Aspergillus* sp., although culture was negative. Ambisome (5 mg/kg/day) was added to the voriconazole treatment (day +22) since we could either be facing an azole-resistant *Aspergillus* sp., or insufficient plasma concentrations resulting in suboptimal cerebral concentrations of voriconazole. PCR analysis targeted at Cyp51A-mediated resistance markers, as described previously [10], was performed using the isolate recovered from sputum and directly on the bronchoalveolar lavage (BAL) sample showing a wild type Cyp51A-gene supporting azole susceptibility. In addition, a presumed adequate intralesional voriconazole concentration of 2.33 mg/L was found. Voriconazole was continued till 3 months after end of chemotherapy (day +477). He fully recovered from his disseminated aspergillosis and is currently in a good clinical condition.

2.2. Case 2

A 2.5-year-old girl, diagnosed with medium risk (MR) ALL, presented with coughing, malaise and febrile neutropenia 1 month after start of chemotherapy. During physical examination of the lungs, bilateral bronchi were noticed. Blood and sputum cultures were taken. Broad spectrum intravenous antibiotics were started according to our local protocol. Four days after presentation, serum GM showed an increased index (GMI) of 6.2. Voriconazole (14 mg/kg/day) i.v. was started immediately (day 0). The next day a HRCT-thorax was performed which showed ground glass aspect areas in both lungs, peribronchial consolidations and a halo sign in the right upper lobe suspect for an invasive fungal infection. A BAL was performed and showed *Aspergillus* sp. by PCR and *A. fumigatus* was cultured. GM index in BAL was 7.4. Susceptibility testing showed an intermediate susceptibility of voriconazole (MIC 2.0 mg/L, determined according EUCAST guideline). Therefore,

trough plasma concentrations of voriconazole were targeted at >3 mg/L keeping in mind the increased chance of toxicity at higher concentrations. Follow-up evaluation (day +21) of the pulmonary abnormalities after 3 weeks of antifungal treatment showed only residual lesions. On day 28 of IV voriconazole treatment the route of administration was switched to oral. Five months later (day +180), while under continued oral voriconazole treatment with varying dosages (based on TDM) the patient was admitted to our hospital with clinical signs of encephalopathy, without focal neurological symptoms, in the presence of a toxic voriconazole plasma concentration of 13.2 mg/L. Voriconazole was immediately ceased for a temporary time period. MRI-cerebrum showed multiple lesions with extensive amounts of edema, especially in the right parietal lobe and the left frontal lobe (Fig. 2). Trepanation of the occipital lesion was performed. The biopsy showed fungal hyphae. Voriconazole level intralesional was 0.6 mg/L, with a plasma concentration of 0.51 mg/L at the time of surgery. *A. fumigatus* (MIC 1 mg/L) was cultured from the cerebrospinal fluid and the GM index was increased (1.4) as well. Since plasma concentrations decreased substantially (as demonstrated in the rapid decline after cessation of voriconazole), antifungal therapy was restarted (day +185) and controlled by intensive TDM. Four months after cessation of the antileukemic treatment, voriconazole treatment was discontinued (day +720). Cerebral and pulmonary imaging show still residual lesions without clinical symptoms.

3. Discussion

We describe two children both presenting with a CNS aspergillosis during treatment for IPA. In our opinion, the dissemination of the IPA to the brain should not be considered as a treatment failure in the presented cases, but infection of the brain most likely has been present at the time IPA was diagnosed. Due to the fact that neurological signs and symptoms were absent, imaging of the brain was not performed initially. In retrospect, the fungal lesions must have been developing during voriconazole treatment for IPA, being an adequate treatment choice, although higher trough concentrations in plasma would have been aimed for. In the latter case we present, the elevated MIC of the *Aspergillus* isolate requires even higher target concentrations and has been complicating optimal treatment. In addition, surgical treatment could have been considered in an earlier stage of disease [11]. This raises the question if earlier screening of the central nervous system

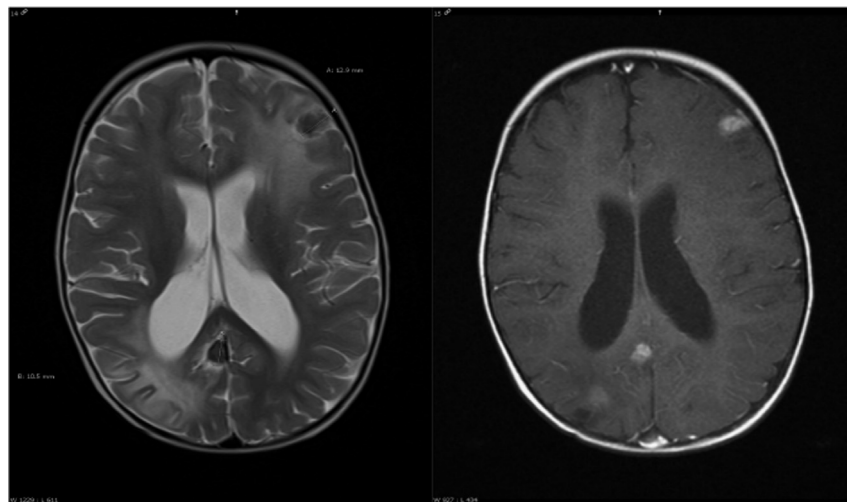


Fig. 1. Patient 1: axial T2 (left) and T1 (right) contrast enhanced MRI-cerebrum show multiple lesions intracerebral at the corticomedullary junction, with low T2 signal with surrounding edema and rim enhancement.

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