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General review

An update on pediatric invasive aspergillosis

Les aspergilloses invasives en pédiatrie

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Abstract

Invasive aspergillosis (IA) is a major cause of morbidity and mortality in immunocompromised adults and children, the number of which has been continuously increasing in the last decades. The purpose of our review was to provide epidemiological, clinical, and biological data and antifungal treatment options in the pediatric population. Several biological assays (galactomannan enzyme immunoassay, β-D-glucan, detection of *Aspergillus* spp. DNA) have proven useful adjuncts for the diagnosis of IA in adult studies. However, data on these assays in children is limited by small sample sizes and sometimes conflicting results concerning their sensitivity/specificity. Pediatric treatment recommendations are mainly extrapolated from results of clinical trials performed in adults. It is thus necessary to develop new antifungal formulations specifically adapted to the pediatric population and to evaluate their pharmacokinetic/pharmacodynamic profile, their safety, and their effectiveness in infants and children.

Keywords: Invasive aspergillosis; Antifungal therapy; Pediatrics

Résumé

L'aspergillose invasive (AI) est une cause majeure de mortalité et de morbidité chez les patients immunodéprimés, dont le nombre est en augmentation régulière au cours des dernières décennies, tant chez les adultes que chez les enfants. Nous présentons ici une revue des données publiées en pédiatrie, en soulignant les particularités cliniques, radiologiques et mycologiques des AI chez l'enfant. Concernant les récents outils diagnostiques mycologiques (détection de l'antigène galactomannane et du (1→3)-β-D glucane, PCR ADN *Aspergillus fumigatus*), les données disponibles en pédiatrie sont encore très parcellaires et parfois discordantes quant à leur sensibilité/spécificité, rendant difficile leur positionnement dans la démarche diagnostique des AI de l'enfant. Les recommandations de traitement prophylactique, préemptif et curatif des AI pédiatriques sont essentiellement extrapolées des données adultes. Des progrès indéniables restent à faire pour développer des formes galéniques d'antifongiques

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adaptées à la pédiatrie, valider leurs posologies par des études pharmacocinétiques chez l'enfant et promouvoir des essais cliniques d'efficacité et de tolérance prenant en compte les spécificités de cette population, notamment pour les plus jeunes enfants (âgés de moins de 2 ans).

Mots clés : Aspergilloses invasives ; Traitement antifongique ; Pédiatrie

The term aspergillus infection includes a wide range of acute and chronic diseases caused by *Aspergillus* spp., filamentous saprophytic fungi in our environment. Invasive aspergillosis (IA) has the most severe prognosis among these diseases with various clinical presentations. It remains a major cause of morbidity and mortality in immunocompromised patients, the number of which has been steadily increasing in recent decades, both in adults and children [1,2]. An increasing number of authors have described the epidemiology and the diagnostic and therapeutic management of IA in adults [3,4]; but few have focused on cases of IA in pediatrics. Zaoutis et al., in a study of this population in 2006, reported a 0.4% yearly incidence of IA in hospitalized immunocompromised children, with 75% of these infections occurring among cancer patients [2].

1. Risk factors for invasive aspergillosis in pediatrics

The main reported risk factors for IA, in pediatric and adult patients, are hematological malignancies [2,5–7] and hematopoietic stem-cell transplantation (HSCT). The risk for IA, in children presenting with a hematological malignancy, depends on the type of blood disease: 3.7 to 28% for acute myelogenous leukemia (AML), 4 to 9% for acute lymphoblastic leukemia relapse (ALL), 0.6 to 2% for de novo ALL [2,7,8]. In case of allogeneic HSCT, the risk is even greater when the donor is unrelated, and it increases with the degree of HLA discrepancy between donor and recipient [1,8 to 10]. The risk also increases in children, as in adults, when graft versus host disease (GVHD) occurs, involving the administration of high-doses of corticosteroids or other immunosuppressive treatments [1,9,10], when neutropenia persists, when the time for immune system reconstitution after transplantation is long, or when there is a concomitant infection caused by the cytomegalovirus or another respiratory virus, or *Aspergillus* colonization [1,9,10].

Other events also predispose to IA [1,10]:

- chemotherapy for lymphoma or solid tumors but in this case the risk is much lower than in case of hematological malignancies. The authors of a pediatric study, Kids Inpatient Database 2000 study, reported an incidence rate of 0.4% for IA cases of lymphoma and 0.1% for solid tumor, compared respectively to 3.7% and 0.6% for of AML and ALL [2];
- solid organ transplantation. IA is a rare complication in this case (except for heart and/or lung transplantation), but it is associated with a high morbidity and mortality rate in children as in adults [11]. The risk is related to the level of immunosuppression, especially for children having undergone lung transplantation [2,5,12];
- primary immune deficiency in the number or function of neutrophils, including aplastic anemia, myelodysplasia, chronic granulomatous disease, immune deficiency by mutation of *STAT3* gene (when aspergillosis occurs on pre-existing lung abnormalities) and *GATA2* gene [2,9,13];
- neonates. The occurrence of IA in neonatology is very rare. However, a few dozen cases have been reported, most frequently in a context of prematurity, chronic granulomatous disease, and/or malnutrition [14].

2. IA mortality in pediatrics

Several authors have suggested a higher IA mortality in children compared with adults. Lin et al. reported an overall mortality of 58% among patients presenting with IA, between 1995 and 2000; but it was 68% in the subgroup of patients < 20 years of age [15]. Walmsley et al. estimated pediatric IA related mortality at 76.9% in a retrospective 10-year single-center series published in 1993 [16]. But these early studies were conducted at a time when the diagnostic and therapeutic tools available above (including using voriconazole for IA) were different from those currently used. Hence the results cannot be directly extrapolated to currently managed patients.

The authors of the largest pediatric study published, included 139 patients treated for IA in 6 US centers, between 2000 and 2005 (most presenting with tumors, treated or not with HSCT); they reported a 52.5% mortality [5]. After multivariate analysis, performing an allogeneic HSCT was identified as an independent risk factor for mortality (OR: 6.58; CI 95% 2.76–16.21). Furthermore, surgical treatment of IA was predictive of survival: the risk of death was 70% lower for surgically treated patients than for the others. Zaoutis et al. in a retrospective study of excess mortality associated with the occurrence of IA in immunocompromised children, hospitalized in the United States in 2000, reported an over-risk ranging from 3.8 in case of allogeneic HSCT, 4.7 in case of solid organ transplantation, 11 in case of leukemia, to 14 in case of solid tumors [2].

3. Clinical presentation of IA in pediatrics

Walmsley et al., in 1993, described 39 cases of IA having occurred at the Toronto Pediatric Hospital for Sick Children (Canada), from 1979 to 1988; they reported 41% of skin lesions and 41% of respiratory lesions [16]. It should be noted that the cases described in this study were associated with IA diagnosed very late, which may have contributed to the particularly high incidence of cutaneous involvements, currently less common thanks to a shorter diagnostic and therapeutic delay. Thus, the