International Journal of Infectious Diseases (2007) 11, 381—393

http://intl.elsevierhealth.com/journals/ijid

REVIEW

Central nervous system aspergillosis in children: a systematic review of reported cases☆

John Dotis, Elias Iosifidis, Emmanuel Roilides*

Third Department of Pediatrics, Aristotle University, Hippokration Hospital, Konstantinoupoleos 49, GR 54642 Thessaloniki, Greece

Received 10 September 2006; received in revised form 9 December 2006; accepted 23 January 2007
Corresponding Editor: J. Peter Donnelly, Nijmegen, The Netherlands

KEYWORDS
Central nervous system aspergillosis;
Neuroaspergillosis;
Children;
Literature review

Summary
Objective: Central nervous system (CNS) aspergillosis is a life-threatening disease that has had a published mortality of >80%. Little is known about this serious infection in the pediatric population. We conducted this study to analyze characteristics of CNS aspergillosis in infants and children.
Methods: The English literature was reviewed and all CNS aspergillosis cases in patients younger than 18 years of age were analyzed.
Results: Ninety cases were recorded up to June 2005. The median age of the patients was 9 years, ranging from 18 days to 18 years (15.6% younger than 1 year). CNS aspergillosis most commonly presented as brain abscess(es), either single or multiple. While prematurity was the predominant underlying condition among infants, leukemia was the most frequent underlying disease in children. *Aspergillus fumigatus* was isolated from 75.5% of the cases. The overall mortality in published cases was 65.4%. In multivariate analysis, surgical treatment was independently associated with survival.
Conclusion: CNS aspergillosis in infants and children predominantly presents as brain abscess(es) and has significantly better outcome compared to published adult data. The findings of this systematic review could assist future investigations for improved outcome of this life-threatening infection in pediatric patients.

Introduction

While novel agents such as amphotericin B lipid formulations, newer azoles and echinocandins have entered the armamentarium of antifungal drugs, invasive aspergillosis (IA) remains a medical challenge due to its very high mortality.[1,2] Invasive aspergillosis predominantly occurs in immunocompromised hosts, such as those with hematological malignancies,

☆ These data were presented in part at the 23rd Annual Meeting of the European Society of Pediatric Infectious Diseases, Valencia, Spain, May 2005 (Abstract 316, p. 160).

* Corresponding author. Tel.: +30 2310 892444; fax: +30 2310 992981.
E-mail address: roilides@med.auth.gr (E. Roilides).

1201-9712/$32.00
doi:10.1016/j.ijid.2007.01.013

hematopoietic stem cell or solid organ transplants, congenital or acquired immunodeficiency, as well as use of corticosteroids and other immunosuppressive drugs.[3] Other situations that predispose to invasive fungal infections including aspergillosis have been found to be intravascular catheters, premature birth, serious burns, abdominal surgery and intravenous drug addiction.[4,5]

Dissemination of *Aspergillus spp* is relatively common, with the central nervous system (CNS) being one of the most frequent sites of IA after the lungs.[6] The brain and subarachnoid space are protected from fungal pathogens by anatomic and functional barriers, but under special conditions and immune system abnormalities, fungal pathogens breach these barriers. CNS symptoms eventually develop in one-half of patients with disseminated aspergillosis and are the presenting feature in one-third of them.[7] The extent of gross neuropathologic disease ranges from subtle abscesses, extensive hemorrhage, focal purulent meningitis and bland infarctions to massive hemorrhagic necrosis causing herniation and death. Despite perceived advances in early diagnosis, initiation of treatment and newer antifungal agents, CNS aspergillosis remains a devastating opportunistic infection, and the prognosis is discouragingly poor in adults.[8]

Invasive aspergillosis in infants and children may exhibit differences from cases in adults, such as less specific findings and greater difficulties in early diagnosis and antifungal treatment.[9] Little is known about CNS aspergillosis in this group of hosts and whether there are any differences from adults. Thus, we conducted a review of all such cases that occurred during childhood that are reported in the literature. Our goal was to review and analyze the pediatric cases in order to determine whether any factor(s), including age, underlying disease, pathological type of and species causing CNS aspergillosis, relationship with other sites of IA, diagnostic methods, and antifungal therapy or adjunctive treatment, affect the outcome of this lethal infection.

Literature review and methods

Relevant case reports and series of CNS aspergillosis published in the English literature were retrieved using 'aspergillosis' and 'central nervous system' as either a keyword or MeSH (medical subject heading) with the limitation 'all child: 0–18 years' from searches of the PubMed bibliographic database (US National Library of Medicine, Bethesda, MD, USA) for the period of 1950 to June 2005. All the articles found by this means were systematically reviewed and a master database was constructed. The references cited in the above articles were screened for additional cases of CNS infections due to *Aspergillus spp* in patients less than 18 years of age.

For this analysis, diagnosis of a definite case of *Aspergillus* CNS infection required evidence of *Aspergillus* in cerebrospinal fluid (CSF) or brain biopsy specimens as either positive culture or histology showing fungal elements. Cases with positive CNS cytology or histology and a positive culture for *Aspergillus* from other site(s) were classified as definite CNS aspergillosis without positive CNS fungal cultures. Cases of patients who had an indication of CNS infection in computed tomography (CT) or magnetic resonance imaging (MRI) scans, plus a definite *Aspergillus* infection at body sites other than the CNS were classified as probable CNS aspergillosis. In addition, the presence of galactomannan antigen or a positive polymerase chain reaction (PCR) test in CSF, or CNS tissue, in the presence of an abnormal CSF showing inflammation in an immunocompromised host, also defined a probable case of *Aspergillus* CNS infection.

Specifically, a definite diagnosis of *Aspergillus* brain abscess required one or more lesions with a hypodense central area and a peripheral uniform ring enhancement following the injection of contrast material attributable to a fungal infection. A variable hypodense area of brain edema as shown by CT or MRI may have surrounded this enhanced ring.[10] *Aspergillus spp* should have been recovered from a culture of aspiration or biopsy of a specimen obtained from the abscess or should have been seen in a biopsy specimen but not cultured or should have indirect evidence of *Aspergillus* infection. Such indirect evidence may have included galactomannan antigen or PCR tests used to define *Aspergillus* meningitis, or be definite or probable at another site in the body (e.g., invasive pulmonary aspergillosis). For such categorization in other sites the criteria constructed by the European Organization for Research and Cancer Treatment Infectious Diseases Group in collaboration with the National Institute of Allergy and Infectious Diseases Mycoses Study Group were used.[11]

Microsoft Excel (XP Professional) software (Redmond, WA, USA) was used to develop a database of categorical and continuous variables. Variables included in the database were demographics such as year of publication of case(s), age and sex of patient(s) and underlying diseases. In addition, diagnostic methods (CT, MRI, galactomannan assay, PCR, culture or histology), pre- or post-mortem diagnosis, type of CNS infection (meningitis, encephalitis, brain abscess, others), prior or concomitant IA affecting other sites of the body, species of *Aspergillus* isolated, antifungal drugs administered, neurosurgery, adjunctive immunotherapy (hematopoietic growth factors, other cytokines, granulocyte transfusions), and outcome were included. The statistical program GraphPad Instat (Graphpad Inc., San Diego, CA, USA) was used for the analysis of the results. Statistical evaluation of differences in proportions and calculation of odds ratio (OR) and 95% confidence intervals (CI) were performed by Fisher's exact test. A p value of <0.05 indicated statistical significance.

Univariate analysis was conducted using the Statistical Package for the Social Sciences for Windows (version 11.5; SPSS Inc., Chicago, IL, USA) to determine the association between potential protective or risk factors (surgery, antifungal therapy, underlying disease, age and year of publication) and survival. All variables with a p value of <0.20 on univariate analysis as well as variables with a biologically plausible relationship were considered for inclusion in a multivariate model. Multivariate analysis was performed using logistic regression.

Results

Seventy-four cases were found in searches of the PubMed bibliographic database as case reports or series. Twenty-two additional cases were found, after the references cited in the above articles were further screened. Six cases were excluded since the authors did not analyze pediatric cases of CNS aspergillosis separately.[12] In parallel, a few additional cases (unspecified number) of pediatric patients aged

between 12 and 18 years were found but no separate analysis was performed, so they were also excluded from the analysis.[13,14] Finally, a total of 90 CNS aspergillosis cases were analyzed. These published cases were for patients younger than 18 years, and for the time period up to June 2005.

The first reported case that was included occurred in 1955 and was published in 1986.[15] It was the case of a 2759 g-birth weight neonate who had suffered from an *Aspergillus* brain abscess. The infant presented with early signs of sepsis requiring intravenous therapy with antibiotics, but infection of the brain due to *Aspergillus spp* occurred 3 weeks later and led to death 30 days later. The cases of CNS aspergillosis in children older than 1 year are summarized in Table 1[16–58] and the cases in infants (less than 1 year of age) in Table 2.[59–61]

Demographic and clinical characteristics

The demographic, clinical and therapeutic characteristics of all the pediatric cases with CNS aspergillosis are shown in Table 3. Fourteen of these patients (14/90, 15.6%) were infants with a median age of 30 days. The median age of older children was 11 years.

Underlying disease

Among infants with an underlying condition reported, prematurity was predominant followed by staphylococcal pneumonia with septicemia, and hepatic failure. Among children (>1 year) with an underlying condition reported, leukemia was the predominant underlying condition, followed by solid tumors, liver transplantation, chronic granulomatous disease (CGD), hematological disorders (e.g., aplasia), and various other conditions. The most common type of leukemia associated with CNS aspergillosis was acute lymphoblastic leukemia (ALL), which was significantly more frequent than acute myelogenous leukemia (AML; including acute non-lymphoblastic leukemia (ANLL)) and chronic myelogenous leukemia (CML) (Table 3 footnote c, $p < 0.05$).

Means of diagnosis and microbiology

Seventy-seven cases were classified as definite according to the definitions mentioned in the Methods section (with or without positive cultures from CNS). Histology and autopsy were the most frequent means of establishing the diagnosis in these cases. In 55 definite cases, complete post- or pre-mortem diagnostic data were available. Stereotactic biopsy cultures from abscesses obtained by craniotomy or percutaneous aspiration of the cerebral lesions grew *Aspergillus spp* in 22 (40%) cases. In two (3.6%) cases the identification of CNS aspergillosis was established by cultures of CSF.[15,29,60,61] In 31 (56.4%) cases CNS aspergillosis was diagnosed post-mortem and in 24 (43.6%) cases diagnosis was established pre-mortem.

Among 53 cases in which *Aspergillus* isolates were identified to the species level, the most frequent species isolated was *Aspergillus fumigatus* followed by *Aspergillus flavus*, *Aspergillus terreus* and *Aspergillus niger* (Table 3).

Pathology

The most common pathological types of CNS aspergillosis were single or multiple brain abscesses throughout the cerebrum, cerebellum, basal ganglia and brainstem. Vasculitis and meningoencephalitis or encephalitis due to *Aspergillus spp* were also found in a few cases (Table 3). The brain lesions consisted of typical necrotizing parenchymal lesions with vascular invasion and secondary hemorrhages, occasionally associated with meningoencephalitis. Hemorrhages most commonly presented as hemorrhagic infarcts, subarachnoid hemorrhages or intracerebral hemorrhages.

Thirty-six cases of CNS aspergillosis presented with additional non-CNS sites of IA. The most common non-CNS affected sites among these cases were the lungs and sinuses, while a number of other sites were additionally involved (Table 3). Multi-organ IA with CNS involvement (three or more organs infected) was found in three cases. In one case, a simultaneous infection of the CNS, lungs, kidney and liver was found; in another case, simultaneous infection was found in the CNS, lungs and liver; and in a third case, simultaneous infection involved the CNS, lung, heart and bone.

Treatment

From a total of 90 reviewed cases with CNS aspergillosis, 42 (46.7%) patients received treatment versus 17 (18.9%) that did not ($p < 0.01$). In the remaining 31 patients data were not available.

The most frequently used drug for the treatment of CNS aspergillosis was amphotericin B, either deoxycholate or lipid formulations of amphotericin B, followed by azoles in some cases. Specifically, among 42 cases with antifungal drug administration reported, amphotericin B (AMB) was used in all cases. Deoxycholate amphotericin B (DAMB) was used as an initial treatment in 35 (83.3%), alone in 13 (31%), combined with flucytosine, rifampin, or with an *Aspergillus*-active azole, itraconazole, in 11 (26.2%), and combined with rifampin plus flucytosine or plus an *Aspergillus*-active azole, itraconazole, in four cases (9.5%). In one case DAMB was combined with fluconazole. In two cases, the primary treatment with DAMB was switched to itraconazole plus flucytosine, and in one case to itraconazole alone. In addition, primary DAMB in one case was switched to amphotericin B lipid complex (ABLC) and then to DAMB, in one case to liposomal amphotericin B (LAMB) and then itraconazole, in one case to LAMB plus itraconazole, and in one case to LAMB plus voriconazole. In one infant case and in four cases in children older than 1 year, rifampin was added to DAMB. Lipid formulations of amphotericin B (in most cases LAMB) were used in 11 (26.2%) cases, alone in two (4.8%), and with an *Aspergillus*-active azole in three cases (7.1%; two itraconazole, one voriconazole). In one case LAMB was combined with fluconazole. Voriconazole was used as monotherapy after discontinuation of DAMB and then LAMB in one case with favorable outcome.[58]

Surgical debridement appears to have a determinant role in the treatment of CNS infections due to *Aspergillus spp* especially of brain abscesses. Surgery was used in 25/69 (36.2%) cases in which information about neurosurgery was provided. On the other hand, granulocyte colony-stimulating factor (G-CSF) was used in 3/42 (7.1%) cases with antifungal therapy reported, interferon-gamma (IFN-γ) in two (4.8%), granulocyte-macrophage colony-stimulating factor (GM-CSF) in two (4.8%), and white blood cell transfusions in one (2.4%) case.

Table 1 Cases of CNS aspergillosis in children older than 1 year sorted by year of diagnosis

Patient	Reference	Year of publication	Sex/age (years)	Underlying disease	Type of CNS infection	Antifungal therapy	Surgery	Outcome
1	16	1962	NA/7	No	Brain abscess	DAMB	Yes	Survived
2	17	1966	F/8	Bacterial infection ⇒ antibiotics— corticosteroid treatment	Brain abscess	No	No	Died
3	18	1971	M/5	ALL	Massive brain abscess	No	No	Died
4	19	1975	F/4	NA	Meningeal and intracerebral arteries invasion	NA	NA	Died
5	19	1975	M/8	NA	Brain abscess	NA	NA	Died
6	19	1975	F/14	NA	Mid-dorsal block invasion	NA	Yes	Survived
7	20	1978	M/18	No	Aspergillosis in the arterial wall	No	No	Died
8	21	1979	M/14	Cellular immunodeficiency	Brain abscess	No	No	NA
9	22	1980	M/7	ALL	Necrotic brain abscess	No	No	Died
10	23	1982	M/12	ALL	Brain abscess	DAMB + 5FC + inhaled natamycin	Yes	Survived
11	24	1982	F/15	Subacute hepatic necrosis	Multiple brain abscesses	No	No	Died
12	25	1983	M/7	Congenital basophil agranulocytocis	Multiple brain abscesses	DAMB + intraventricular DAMB	No	Died
13	26	1985	M/9	Hepatic failure	Multiple brain abscesses	No	No	Died
14	26	1985	M/14	ALL	Multiple brain abscesses	No	No	Died
15	27	1987	M/4	CGD	Epidural abscess	DAMB + 5FC	Yes	Survived
16	28	1988	M/10	ALL (T-Cell)	Infarction with invasion	DAMB	No	Died
17	29	1989	M/5	Liver transplantation	Meningoencephalitis	NA	No	Died
18	29	1989	F/11	Liver transplantation	Meningoencephalitis	NA	No	Died
19	29	1989	M/18	Liver transplantation	Meningoencephalitis	NA	No	Died
20	30	1991	M/11	CGD	Intracerebral lesions	DAMB ⇒ itraconazole + 5FC + WBCTx	No	Survived
21	31	1993	F/2	CGD	Brain abscess	NA	Yes	NA
22	32	1993	F/6	Pre-B-ALL + BMT	Multiple brain abscesses	DAMB ⇒ itraconazole	Yes	Survived
23	33	1993	M/16	Heart transplantation	Occipital and parietal infracts due to *Aspergillus*	NA	NA	NA
24	33	1993	M/18	Liver transplantation	Multiple brain abscesses	NA	NA	NA
25	33	1993	F/18	Liver transplantation	Occipital hemorrhagic infracts	NA	NA	NA
26	34	1994	M/10	ALL	Multifocal cerebral aspergillosis	DAMB ⇒ itraconazole + 5FC	No	Survived
27	35	1995	M/2	ALL	Multiple brain abscesses	DAMB ⇒ LAMB ⇒ oral itraconazole	Yes	Survived
28	36	1995	M/2	HIV	Brain abscess	DAMB	NA	Died
29	36	1995	M/12	HIV	Encephalopathy	No	No	Died
30	37	1996	F/17	Prior (15 months) surgical treatment for an ependymoma	Brain abscess	DAMB + itraconazole	Yes	Died
31	38	1997	F/14	ALL + HSCT	Multiple brain abscesses	DAMB ⇒ ABLC ⇒ DAMB	No	Survived

32	39	1997	F/18	BMT for aplastic anemia	Brain abscess	LAMB + itraconazole	Yes	Survived
33	40	1998	NA/14	ALL	Aspergillosis in the vessel wall	NA	NA	NA
34	40	1998	NA/14	AML	Paravertebral mass, cord infarct due to *Aspergillus*	NA	NA	NA
35	40	1998	F/15	ALL	Multifocal purulent leptomeningeal exudates, abscess in cord	DAMB	NA	NA
36	41	1998	NA/<18	CML	Multiple brain abscesses	NA	No	Died
37	41	1998	NA/<18	PNET	Multiple brain abscesses	NA	Yes	Died
38	41	1998	NA/<18	ALL	Multiple brain abscesses	NA	No	Died
39	41	1998	NA/<18	Glioma	Brain abscess	NA	Yes	Survived
40	41	1998	NA/<18	AML	Multiple brain abscesses	NA	No	Survived
41	41	1998	NA/<18	Glioma	Brain abscess	NA	Yes	Survived
42	41	1998	NA/<18	AML	Brain abscess	NA	Yes	Died
43	42	1999	F/10	Neurosurgery for craniopharyngioma	Intracerebral hemorrhage due to *Aspergillus* invasion	No	Yes	Died
44	43	1999	F/11	ALL	Vasculitis + multiple brain abscesses	DAMB	Yes	Died
45	44	1999	M/17	ANLL	NA	DAMB	No	Died
46	44	1999	M/9	ANLL	NA	No	No	Died
47	44	1999	F/16	ANLL	NA	DAMB + rifampin + 5FC	Yes	Died
48	44	1999	F/14	ALL	NA	DAMB + rifampin + 5FC + GM-CSF	No	Died
49	44	1999	F/11	MDS + BMT	NA	DAMB + rifampin + 5FC	No	Died
50	44	1999	F/3	ANLL	NA	DAMB	No	Died
51	44	1999	M/16	ALL	NA	DAMB + 5FC	No	Died
52	44	1999	M/16	ALL + BMT	NA	DAMB + rifampin + itraconazole	No	Died
53	44	1999	F/14	Hodgkin's lymphoma	NA	DAMB	No	Died
54	44	1999	F/1 (13 months)	Neuroblastoma	NA	No	No	Died
55	44	1999	M/18	ANLL + BMT	NA	DAMB	No	Died
56	44	1999	M/2	ANLL + BMT	NA	No	No	Died
57	44	1999	M/3	ALL	NA	DAMB	No	Died
58	44	1999	F/15	MDS + BMT	NA	DAMB + 5FC	No	Died
59	45	1999 (diagnosis in 1992)	M/17	ALL	NA	DAMB + 5FC	Yes	Survived
60	45	1999 (diagnosis in 1992)	M/16	ALL	NA	Fluconazole ⇒ DAMB + 5FC + G-CSF	No	Died
61	46	2000	F/2	ALL (B-cell)	Brain abscess	LAMB + fluconazole + G-CSF	Yes	Survived
62	47	2000	M/4	Hurler disease	NA	NA	NA	Died
63	47	2000	F/5	Fanconi anemia	NA	NA	NA	Died
64	47	2000	M/11	Aplastic anemia	NA	NA	NA	Survived
65	48	2001	F/5	Cardiomyopathy	Multiple brain abscesses	NA	NA	NA

Table 1 (*Continued*)

Patient	Reference	Year of publication	Sex/age (years)	Underlying disease	Type of CNS infection	Antifungal therapy	Surgery	Outcome
66	48	2001	F/5	Crouzon syndrome, post-surgical infection	Multiple brain abscesses	NA	NA	Survived
67	49	2001	M/11	CGD	Brain abscess	DAMB + itraconazole + IFN-γ	Yes	Survived
68	50	2001	F/16	AML	Spinal epidural abscess	DAMB	Yes	Survived
69	51	2002	F/10	Cardiomyopathy, heart transplantation	Cerebral artery-focal *Aspergillus* vasculitis	No	No	Died
70	52	2002	M/11	Alveolar rhabdomyosarcoma ⇒ chemotherapy	Multiple brain abscesses	LAMB	No	Survived
71	53	2003	M/7	Craniocerebral injury	Brain abscess	DAMB ⇒ LAMB + itraconazole	Yes	Survived
72	54	2003	F/11	AML + BMT	Cortical vessels thrombosis by *Aspergillus* invasion	DAMB + fluconazole	No	Died
73	55	2003	M/2	Corticosteroid-resistant nephrotic syndrome	Encephalitis	LAMB	No	Died
74	56	2003	M/12	Alopecia areata ⇒ corticosteroid treatment	Brain abscess	LAMB ⇒ itraconazole	Yes	Survived
75	57	2004	F/3	ALL	Orbitocerebral aspergillosis	LAMB + 5FC ⇒ LAMB + voriconazole + G-CSF + IFN-γ + GM-CSF	No	Survived
76	58	2006	M/8	CGD	Multiple brain abscesses	DAMB ⇒ LAMB ⇒ voriconazole	No	Survived

CNS, central nervous system; M, male; F, female; NA, not available; AMB, amphotericin B; DAMB, deoxycholate amphotericin B; LAMB, liposomal amphotericin B; ABLC, amphotericin B lipid complex; 5FC, flucytosine; WBCTx, white blood cell transfusion; ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; PNET, primitive neuroectodermal tumor; MDS, myelodysplastic syndrome; BMT, bone marrow transplantation; CGD, chronic granulomatous disease; HSCT, hematopoietic stem cell transplantation; HIV, human immunodeficiency virus; IFN-γ, interferon-gamma; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte—monocyte colony-stimulating factor.

Table 2 Cases of CNS aspergillosis in infants sorted by year of diagnosis

Patient	Reference	Year of publication	Sex/age (days)	Underlying disease	Type of CNS infection	Antifungal therapy	Surgery	Outcome
1	15	1986 (diagnosis in 1955)	NA/30	Staphylococcal sepsis	Brain abscess	No	No	Died
2	15	1986 (diagnosis in 1957)	NA/25	Broad spectrum antibiotics	Brain abscess	No	No	Died
3	15	1986 (diagnosis in 1963)	NA/51	*Escherichia coli* sepsis	Brain abscess	No	No	Died
4	15	1986 (diagnosis in 1985)	NA/27	Prematurity	Brain abscess	DAMB + 5FC + intraventricular DAMB	Yes	Survived
5	59	1991	M/98	Liver transplantation	Brain abscess	DAMB + rifampin + intraventricular DAMB	Yes	Survived
6	60	1998 (diagnosis in 1963)	F/51	Prematurity, erythroblastosis fetalis, recurrent bacteremia	NA	NA	NA	Died
7	60	1998 (diagnosis in 1963)	F/59	Prematurity	NA	NA	NA	Died
8	60	1998 (diagnosis in 1966)	F/73	Diarrhea, dehydration	NA	NA	NA	Died
9	60	1998 (diagnosis in 1973)	M/65	Staphylococcal septicemia, pneumonia	Diffuse meningoencephalitis	NA	NA	Died
10	60	1998 (diagnosis in 1979)	F/18	Hepatic failure	NA	NA	NA	Died
11	60	1998 (diagnosis in 1988)	F/24	Hepatic failure	NA	NA	NA	Died
12	60	1998 (diagnosis in 1989)	F/22	Malnutrition	NA	NA	NA	Died
13	60	1998 (diagnosis in 1992)	M/29	Cyanotic heart disease	Multiple brain abscesses	DAMB	Yes	Survived
14	61	2000	M/30	Aplastic cutis congenita at the scalp vertex + hypoplastic left heart syndrome	Multiple brain abscesses	LAMB + 5FC	No	Survived

CNS, central nervous system; M, male; F female; NA, not available; DAMB, deoxycholate amphotericin B; LAMB, liposomal amphotericin B; 5FC, flucytosine.

Table 3 Characteristics of reviewed cases of CNS aspergillosis in childhood ($N = 90$)

Age of all patients (median, range)	9 years (18 days—18 years)
Age of infants ($n = 14$)	30 days (18 days—98 days)
Age of older children ($n = 76$)	11 years (1 year—18 years)
Male sex ($n = 76$)	41 (53.9%)
Underlying disease in infants[a] ($n = 14$)	
Prematurity	3 (21.4%)
Staphylococcal infection[b]	2 (14.3%)
Hepatic failure	2 (14.3%)
Underlying disease in patients >1 year[a] ($n = 73$)	
Leukemia[c]	33 (45.2%)
Solid tumors	7 (9.6%)
Liver transplantation	5 (6.8%)
CGD	5 (6.8%)
Diagnosis of definite cases ($n = 55$[d])	
Post-mortem	31 (56.4%)
Pre-mortem	24 (43.6%)
Biopsy cultures	22 (40%)
Blood/CSF cultures	2 (3.6%)
Aspergillus species identity ($n = 53$)	
Aspergillus fumigatus	40 (75.5%)
Aspergillus flavus	10 (18.9%)
Aspergillus terreus	2 (3.8%)
Aspergillus niger	1 (1.8%)
Type of *Aspergillus* infection[a] ($n = 65$)	
Brain abscess(es)	45 (69.2%)
Vasculitis	10 (15.4%)
Meningoencephalitis/encephalitis	5 (7.7%)
Non-CNS sites of *Aspergillus* infection[a] ($n = 36$)	
Lungs	22 (61.1%)
Sinuses	4 (11.1%)
Kidneys	2 (5.6%)
Liver	2 (5.6%)
Other sites	6 (16.7%)
Antifungal therapy ($n = 59$)	
No treatment	17 (28.8%)
Antifungal treatment	42 (71.2%)
Amphotericin B	42 (100%)
(Deoxycholate amphotericin B[e])	35
(Lipid formulations of amphotericin B[f])	11
Voriconazole	2 (4.8%)
Surgery[a] (intralesional debridement, $n = 69$)	25 (36.2%)

CNS, central nervous system; CGD, chronic granulomatous disease; CSF, cerebrospinal fluid.

[a] Most frequent entities.

[b] Pneumonia/sepsis.

[c] Acute lymphoblastic leukemia 21/33 (63.6%), acute myelogenous leukemia (including acute non-lymphoblastic leukemia) and chronic myelogenous leukemia 12/33 (36.4%) ($p < 0.05$).

Mortality of CNS aspergillosis

The overall mortality rate in this cohort of published pediatric cases of CNS aspergillosis was 65.4% (Table 4). However, the overall mortality rate of the cases reported after 1990 (with known year of diagnosis) was 39.5%, whilst that of the cases reported before 1990 was 82.8% ($p = 0.0004$). Specifically, cases that occurred in children >1 year old and published after 1990 had a significantly lower mortality rate than cases reported before 1990 ($p = 0.021$). Similarly, cases that occurred in infants and published after 1990 had a significantly lower mortality rate than cases reported before 1990 ($p = 0.01$).

There was no difference between the periods after 1998 and 1990—1998. While after 1998 overall mortality was 38.9% (7/18 cases), between 1990 and 1998 it was 40% (8/20 cases), and before 1990 it was 82.8% (24/29 cases). Various other time breakpoints did not show significant differences on mortality rates.

When single case reports were separated from case series (defined as containing at least two originally reported cases), the overall mortality rate of case series was 71.2%. The mortality rate of the case series reported after 1990 was 52.9%, whilst that of the case series reported before 1990 was 90.5% ($p = 0.023$) (Table 4).

When the mortality was determined only for the smaller number of cases that were diagnosed pre-mortem, there was an insignificant trend of lower mortality rate after combined surgical and antifungal treatment as compared to antifungal drugs alone and no neurosurgery. Similarly, there was a trend for higher mortality induced by *A. flavus* than by *A. fumigatus* in the small number of cases with pathogen identification to the species level (Table 4).

Before 1990, although the outcome was reported, data on antifungal therapy were available only in some cases. After 1990 the antifungal therapy data were available in 18 survivors. In this period, DAMB was the initial therapy in 12 survivors (66.7%) and LAMB in six (33%). Amphotericin B plus an *Aspergillus*-active azole either as initial therapy or secondary therapy was used in four patients (22.2%; three itraconazole (two plus LAMB, one plus DAMB), one voriconazole (one plus LAMB)).

Fifty-six infants and children with all data included in the original publication were enrolled in a univariate analysis of

[d] Number of definite cases with post- or pre-mortem data available.

[e] Alone in 13 cases (31%), combined with flucytosine, rifampin, or with an *Aspergillus*-active azole, itraconazole, in 11 (26.2%) and combined with rifampin plus flucytosine or plus an *Aspergillus*-active azole, itraconazole, in four (9.5%). The primary treatment with deoxycholate amphotericin B (DAMB) was switched in two cases to itraconazole plus flucytosine, in one cases to itraconazole alone, in one case to amphotericin B lipid complex and switched again to DAMB, in one case to liposomal amphotericin B (LAMB) and then itraconazole, in one case to LAMB plus itraconazole, and in one case to LAMB plus voriconazole. In one infant and in four children older than 1 year, DAMB was used in combination with rifampin.

[f] Alone in two (4.8%) patients, combined with *Aspergillus*-active azoles like itraconazole (2) or voriconazole (1) in three (7.1%) patients.

Table 4 Mortality of CNS aspergillosis

Overall mortality rate (n = 81)	53 (65.4%)
Prior to 1990 (n = 29)	24 (82.8%)[a]
Infants (<1 year) (n = 11)	10 (90.9%)[b]
Children (>1 year) (n = 18)	14 (77.8%)[c]
After 1990[d] (n = 38)[e]	15 (39.5%)[a]
Infants (n = 3)	0 (0%)[b]
Children (n = 35)	15 (42.9%)[c]
Mortality rate in case series reports (n = 59)	42 (71.2%)[f]
Prior to 1990 (n = 21)	19 (90.5%)[g]
Infants (n = 11)	10 (90.9%)[h]
Children (n = 10)	9 (90%)[i]
After 1990 (n = 17)[e]	9 (52.9%)[g]
Infants (n = 1)	0 (0%)[h]
Children (n = 16)	9 (56.3%)[i]
Mortality rate in single case reports (N = 29)	11 (37.9%)[f]
Prior to 1990 (n = 8)	5 (62.5%)[j]
Infants (n = 0)	—
Children (n = 8)	5 (62.5%)[k]
After 1990 (n = 21)	6 (28.6%)[j]
Infants (n = 2)	0 (0%)
Children (n = 19)	6 (31.6%)[k]
Mortality rate in cases diagnosed pre-mortem	
With antifungal therapy only (n = 10)	3 (30%)[l]
With antifungal therapy and surgical treatment (n = 16)	2 (12.5%)[l]
Mortality rate in cases according to *Aspergillus spp*	
A. fumigatus (n = 38)	20 (52.6%)[m]
A. flavus (n = 10)	8 (80%)[m]

n, number of patients with individual data reported.

[a] Between mortality rates prior to 1990 and after 1990, OR: 0.14, 95% CI: 0.042—0.43, p = 0.0004.

[b] Between mortality rates prior to 1990 and after 1990 in infants, OR: 0.02, 95% CI: 0.0007—0.63, p = 0.01.

[c] Between mortality rates prior to 1990 and after 1990 in children, OR: 0.21, 95% CI: 0.059—0.78, p = 0.021.

[d] After 1990 the antifungal therapy data were available for 18 survivors. In this period, deoxycholate amphotericin B (DAMB) was the initial therapy in 12 survivors (66.7%) and liposomal amphotericin B (LAMB) in six (33%). Amphotericin B plus an *Aspergillus*-active azole either as initial therapy or secondary therapy was used in four (22.2%) patients (three itraconazole (two plus LAMB, one plus DAMB), one voriconazole (one plus LAMB)).

[e] Data coming from cases with known year of diagnosis (cases from Ref. 44 are not included).

[f] Between mortality rates based on single case reports and case series reports, OR: 0.25, 95% CI: 0.097—0.63, p = 0.005.

[g] Between mortality rates (based on case series reports) prior to 1990 and after 1990, OR: 0.12, 95% CI: 0.02—0.68, p = 0.023.

[h] Between mortality rates (based on case series reports) prior to 1990 and after 1990 in infants, OR: 0.048, 95% CI: 0.001—1.8, p = 0.17.

[i] Between mortality rates (based on case series reports) prior to 1990 and after 1990 in children, OR: 0.14, 95% CI: 0.015—1.41, p = 0.099.

[j] Between mortality rates (based on single case reports) prior to 1990 and after 1990, OR: 0.24, 95% CI: 0.04—1.34, p = 0.198.

[k] Between mortality rates (based on single case reports) prior to 1990 and after 1990 in children, OR: 0.28, 95% CI: 0.049—1.56, p = 0.21.

[l] Between mortality rates of cases that were diagnosed pre-mortem and had surgical treatment combined with antifungal treatment and cases that were managed with antifungal drugs only and no neurosurgery, OR: 3, 95% CI: 0.4—22, p = 0.34.

[m] Between mortality rates of cases that *A. fumigatus* and *A. flavus* was isolated, OR: 0.28, 95% CI: 0.05—1.5, p = 0.16.

factors potentially associated with survival of the patients (Table 5). Surgery and antifungal therapy were found to be significant protective factors, whereas age >1 year or leukemia as underlying disease were not associated with altered survival. Furthermore, among 49 patients older than 1 year, surgery and the antifungal therapy were significant factors ($p < 0.01$) associated with survival of the patients (data not shown). However, of these factors only surgery was independently associated with survival when included in multivariate analysis models (OR: 10, 95% CI: 2—50, p = 0.0048).

Discussion

In this study we analyzed the characteristics of a large number of pediatric cases of CNS aspergillosis published as single case reports, small series, or as part of larger series. We found that most cases presented as single or multiple brain abscesses, with *A. fumigatus* being the most frequent cause. The predominant underlying condition was prematurity among infants and leukemia among children. Together with antifungal therapy, surgery was associated with significantly improved outcome.

Historically, the mortality rate of CNS aspergillosis was exceeding 90% and even approaching 100% in adult patients with acute leukemia with or without bone marrow transplantation; this decreased to no lower than approximately 70% even in the last published study after administration of voriconazole with or without surgery.[2,8,62] Such data, however, were lacking for pediatric patients. The better outcome of CNS aspergillosis in infants and children that we found (39.5% mortality in cases published after 1990) reflects the overall more favorable prognosis of IA in children than in adults.[48,60] This discrepancy may be related to different underlying diseases in the two age groups and other coexisting conditions as well as other age-related differences not clearly defined at present. For example, the better outcome in children may be related to the generally better prognostic outlook of their underlying conditions (i.e., acute leukemia). Publication bias (i.e., cases of non-surviving patients possibly not being 'reportable' during the last decade) may have potentially underestimated mortality in our analysis. However, the same publication bias applies for similarly published adult cases. Thus, the mortality difference between pediatric patients and adults is most probably true.

This comprehensive analysis of all pediatric cases of CNS aspergillosis published in the English literature up to June 2005 indicates a substantial decrease in mortality from 82.8% before 1990 to less than half (39.5%) in cases published after 1990. This dramatic decrease in infants and children may have been due to the introduction of amphotericin B lipid formulations and *Aspergillus*-active azoles as well as most importantly to the developments for earlier diagnosis of CNS aspergillosis. Strengthening the validity of this finding, mortality was also decreased from 90.5% before 1990 to 52.9%

Table 5 Potential protective factors for survival of patients during univariate analysis[a]

Characteristic	Survival				
	Yes (n = 22)	No (n = 34)	OR	95% CI	p Value
Surgery (%)	68	12	16	4.06—63.65	<0.0001
Antifungal therapy (%)	100	53	40	2.25—715	<0.0001
Age (more than 1 year) (%)	82	91	0.436	0.087—2.17	0.415
Leukemia as underlying disease (%)	41	50	0.69	0.23—2.047	0. 589

[a] Fifty-six infants and children with all data available.

after 1990 (p = 0.023) when single case reports, where publication bias is believed to be a larger problem than in cases series reports, were excluded (Table 4). While only a trend of decreased mortality rate in the published cases that had combined surgical and antifungal drug treatment (12.5%) was observed compared to antifungal drugs alone (30%, p = 0.34), in cases with localized lesions of CNS, such as brain abscesses, neurosurgery may be associated with a favorable outcome of the patients.

Aspergillus spp can induce unusual clinical features caused by unique sites of CNS involvement. Specifically, basilar meningitis, myelitis, sino-orbital disease, carotid artery invasion, epidural abscesses, massive hemorrhagic necrosis with herniation as the cause of death, isolated or subtle intracranial disease, and mycotic aneurysms can be caused by *Aspergillus spp*. In addition, hemorrhagic necrosis as the primary macroscopic feature of CNS aspergillosis has been emphasized in some studies.[33,48] In this review, single or multiple brain abscesses were the most common sites of CNS aspergillosis and were found in 45/65 (69.2%) cases.

Aspergillus spp are primarily respiratory pathogens, and the lungs constitute the main portal of entry before dissemination. It is important to note that in most cases of CNS aspergillosis the portal of entry and the route for *Aspergillus spp* remains unspecified and is a subject of speculation. However, in 45% (9/20) of the reviewed cases with data available, CNS aspergillosis was the result of dissemination from the respiratory tract. In a few cases, CNS constitutes the primary site involved in aspergillosis.

Underlying disease seems to be a very important factor for the development of CNS aspergillosis. Prematurity is a risk factor for neonatal IA suggesting that immature neonatal anatomical and immune defense systems probably play a role in disease acquisition.[60] Supporting this notion, in this review we found that in infants, prematurity was the predominant underlying disease in 21.4% of reported cases. Among three infants with prematurity as underlying disease and gestational age mentioned, gestational age ranged from 31 to 32 weeks; there was no apparent trend of difference in mortality according to the gestational age. In addition, in neonates catheter-related infection is theoretically possible, but this cannot be documented by blood culture in most of the cases. In adults, CNS aspergillosis is more often associated with immunosuppressive therapy.[7,48] One report suggested that premature infants exhibit higher risk to present with CNS aspergillosis than infants receiving immunosuppressive drugs.[15] Our finding that staphylococcal infection followed prematurity as underlying disease is likely to be due to undiagnosed CGD in these infants.

Our study demonstrated that the most common underlying diseases associated with CNS aspergillosis in children older than 1 year are hematological malignancies, with the majority of patients having leukemia, most commonly ALL followed by AML. The incidence of proven or probable invasive aspergillosis is greater in children with AML (27.7%) than in children with ALL (2%);[45] however, AML accounts for only about 15—20% of cases of childhood leukemia and ALL for about 75%.[63]

In the children with leukemia, the major risk factor for developing CNS aspergillosis is severe neutropenia secondary to chemotherapy.[2] Neutropenia and corticosteroids may synergistically act to depress natural host defenses.[64] While there was no specific data in all the cases with regard to neutropenia, we can infer that most children with leukemia and IA developed the infection during neutropenia. In contrast, patients with CGD as underlying disease did not usually have neutropenia as risk factor for IA. In patients with other underlying conditions such as premature neonates and liver transplantation patients, information about neutropenia was not always given. The meta-analytic character of the study did not allow us to collect all these data.

Solid organ transplantation is also a significant predisposing condition, illustrating the importance of immunosuppression for the development of CNS aspergillosis. Some investigators have found that in this population, the majority of CNS aspergillosis occurred within the first 3 months after transplantation, which is the most critical period for IA. Liver transplant recipients were reported to have earlier onset of symptoms compared with other transplant recipients. Increased incidence for CNS aspergillosis can be observed after the first year of transplantation during chronic rejection and/or retransplantation during intense immunosuppresion.[33,65]

This systematic review of the previously published cases shows that in agreement with the fact that *A. fumigatus* is the most common isolate obtained in 70—90% of cases of IA in immunocompromised patients, this species is also the most frequent cause of CNS aspergillosis.[9,48,66] Of note, *A. flavus* constitutes the second most common species, having been isolated from 18.9% of cases with reported data. The observed higher mortality induced by *A. flavus* was not significant.

Despite recent advances in non-invasive surrogate markers of many diseases, radiological evaluation remains the cornerstone of diagnosing IA and CNS aspergillosis.[54,67] Unfortunately, in 56.4% (31/55) of CNS aspergillosis cases reported, diagnosis was established only at autopsy (22 cases before and nine after 1990). New antigen tests for the early diagnosis of IA, such as the galactomannan ELISA assay, have been plagued by lower sensitivity and specificity in certain

populations of pediatric patients.[9,68,69] The use of the galactomannan assay for the diagnosis of CNS aspergillosis has been reported,[70] but warrants further investigations.

Amphotericin B has been the mainstay of medical treatment for both suspected and proven CNS aspergillosis in childhood during the last decades. DAMB appears to be well tolerated in infants <3 months without significant nephrotoxicity.[60,71] However, in older patients poor tolerability often leads to the use of other *Aspergillus*-active antifungal agents, such as lipid formulations of amphotericin B, itraconazole and more recently voriconazole. To date, it has not been established whether itraconazole or lipid formulations of amphotericin B have superior efficacy to DAMB.[62,72] However, some patients refractory to, or intolerant of DAMB have responded to itraconazole or to lipid formulations of amphotericin B. Due to the retrospective nature of our review the issue of dosing of antifungal agents could not be addressed.

The fact that colony-stimulating factors, such as G-CSF and GM-CSF as well as cytokines, such as IFN-γ, have been administered to only few pediatric patients with CNS aspergillosis does not permit us to draw any definitive conclusions about the potential role of adjunctive immunotherapy in such patients. However, it is reasonable to speculate that restoration or augmentation of immune responses in these patients would be useful, and these strategies deserve additional study.[73]

Recently, voriconazole treatment has been reported to improve outcome of CNS aspergillosis from historical survival rates of <10%[1,62] to a rate of 31% in a cohort of 81 previously studied cases including a few pediatric patients.[8] Among six such cases of pediatric patients with ages ranging from 9 months to 15 years treated with voriconazole, three had complete or partial response, one remained in a stable condition and two patients died.[12] Since the authors of this report did not analyze pediatric cases of CNS aspergillosis separately, we could not include these children in our study. A few additional cases of pediatric patients aged between 12 and 18 years, treated with voriconazole, are also included in two other studies,[13,14] but again no separate analysis was performed. Indeed, the findings of this systematic review of published pediatric CNS aspergillosis cases could assist future investigations for improved outcome of this life-threatening infection.

There are some limitations to this study due to the fact that the conclusions may be wrong if the cases analyzed are not a representative sample due to publication bias. Thus, early cases (1970s and 1980s) may have been reported because of their uniqueness regardless of outcome, whereas cases reported in the subsequent decade (1990s) may have been published rather with a focus on therapeutic success. In order to confront the publication bias we could potentially include only reports with a minimum number of cases. However, since CNS aspergillosis is a rare disease we would exclude most of the data on this entity. Therefore, we preferred to use the single case reports for demographic analysis, but we excluded them from the analysis of the effect of publication year on the mortality. In addition, concerning the association of neurosurgery and favorable outcome, it might be the case that those patients deemed likely to do well received surgery whereas the very sick and 'hopeless' patients were not considered appropriate for surgery. Obviously, a randomized study is not appropriate and feasible in these patients, a problem inherent also in other recent studies.[8]

In conclusion, despite its limitations this review suggests that the outcome of CNS aspergillosis in infants and children is better than in adults and may have been further improved after the introduction of antifungal agents with better therapeutic profile and the use of better diagnostic modalities. The recent introduction of novel *Aspergillus*-active azoles coupled with efforts for early and more accurate diagnosis of IA in young patients[69] may further improve the outcome of this life-threatening infection.

Acknowledgments

We thank Charalampos Antachopoulos, MD, PhD, for his review and his thoughtful comments on the manuscript. No financial support was granted for the study.

Conflict of interest: No conflict of interest to declare.

References

1. Patterson TF, Kirkpatrick WR, White M, Hiemenz JW, Wingard JR, Dupont B, et al. Invasive aspergillosis: disease spectrum, treatment practices, and outcomes. *Medicine (Baltimore)* 2000;**79**:250—60.
2. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis* 2001;**32**:358—66.
3. Kontoyiannis DP, Bodey GP. Invasive aspergillosis in 2002: an update. *Eur J Clin Microbiol Infect Dis* 2002;**21**:161—72.
4. Groll AH, Walsh TJ. Uncommon opportunistic fungi: new nosocomial threats. *Clin Microbiol Infect* 2001;**7**:8—24.
5. Tietz HJ, Martin H, Koch S. Incidence of endomycoses in autopsy material. *Mycoses* 2001;**44**:450—4.
6. Denning DW. Invasive aspergillosis. *Clin Infect Dis* 1998;**26**:781—803.
7. Boes B, Bashir R, Boes C, Hahn F, McConnell JR, McComb R. Central nervous system aspergillosis: analysis of 26 patients. *J Neuroimag* 1994;**4**:123—9.
8. Schwartz S, Ruhnke M, Ribaud P, Corey L, Driscoll T, Cornely OA, et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. *Blood* 2005;**106**:2641—5.
9. Steinbach WJ. Pediatric aspergillosis: disease and treatment differences in children. *Pediatr Infect Dis J* 2005;**24**:358—64.
10. Mathisen GE, Johnson JP. Brain abscess. *Clin Infect Dis* 1997;**25**:763—81.
11. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002;**34**:7—14.
12. Walsh TJ, Lutsar I, Driscoll T, Dupont B, Roden M, Ghahramani P, et al. Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. *Pediatr Infect Dis J* 2002;**21**:240—8.
13. Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis* 2002;**34**:563—71.
14. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;**347**:408—15.
15. Rhine WD, Arvin AM, Stevenson DK. Neonatal aspergillosis. A case report and review of the literature. *Clin Pediatr* 1986;**8**:400—3.

16. Conen PE, Walker GR, Turner JA, Field P. Invasive primary aspergillosis of the lung with cerebral metastasis and complete recovery. *Dis Chest* 1962;**42**:88—94.
17. Hughes WT. Generalized aspergillosis. A case involving the central nervous system. *Am J Dis Child* 1966;**112**:262—5.
18. Amromin GD, Gildenhorn VB. Massive cerebral *Aspergillus* abscess in a leukemic child. Case report. *J Neurosurg* 1971;**35**: 491—4.
19. Deshpande DH, Desai AP, Dastur HM. Aspergillosis of the central nervous system. A clinical and mycopathological study of 9 cases. *Neurology India* 1975;**23**:167—75.
20. Mohandas S, Ahuja GK, Sood VP, Virmani V. Aspergillosis of the central nervous system. *J Neurol Sci* 1978;**38**:229—33.
21. Tully RJ, Watts C. Computed tomography and intracranial aspergillosis. *Neuroradiology* 1979;**17**:111—3.
22. Masera G, Scotti G, Uderzo C, Auriti L, Perrone P, de Grandi C, et al. Cerebral aspergillosis in a child with acute lymphoblastic leukaemia. A case report. *Haematologica* 1980;**65**:773—9.
23. Henze G, Aldenhoff P, Stephani U, Grosse G, Kazner E, Staib F. Successful treatment of pulmonary and cerebral aspergillosis in an immunosuppressed child. *Eur J Pediatr* 1982;**138**:263—5.
24. Beal MF, O'Carroll CP, Kleinman GM, Grossman RI. Aspergillosis of the nervous system. *Neurology* 1982;**32**:473—9.
25. Galli G, Gandolfini M, Lenzi A, Gatta G, Marini G. Intraventricular and intravenous use of amphotericin B in a case of non-surgical cerebral aspergillosis. *J Neurosurg Sci* 1983;**27**:59—61.
26. Walsh TJ, Hier DB, Caplan LR. Aspergillosis of the central nervous system: clinicopathological analysis of 17 patients. *Ann Neurol* 1985;**18**:574—82.
27. Pollack IF, Pang D, Schuit KE. Chronic granulomatous disease with cranial fungal osteomyelitis and epidural abscess. Case report. *J Neurosurg* 1987;**67**:132—6.
28. Barrios N, Tebbi CK, Rotstein C, Siddiqui S, Humbert JR. Brainstem invasion by *Aspergillus fumigatus* in a child with leukemia. *N Y State J Med* 1988;**88**:656—8.
29. Hall WA, Martinez AJ. Neuropathology of pediatric liver transplantation. *Pediatr Neurosci* 1989;**15**:269—75.
30. Kloss S, Schuster A, Schroten H, Lamprecht J, Wahn V. Control of proven pulmonary and suspected CNS *Aspergillus* infection with itraconazole in a patient with chronic granulomatous disease. *Eur J Pediatr* 1991;**150**:483—5.
31. Dean AF, Janota I, Thrasher A, Robertson I, Mieli-Vergani G. Cerebral aspergilloma in a child with autosomal recessive chronic granulomatous disease. *Arch Dis Child* 1993;**68**:412—4.
32. Trigg ME, Menezes AH, Giller R, Lanza L, Smith RJ, Sato Y, et al. Combined anti-fungal therapy and surgical resection as treatment of disseminated aspergillosis of the lung and brain following BMT. *Bone Marrow Transplant* 1993;**11**:493—6.
33. Torre-Cisneros J, Lopez OL, Kusne S, Martinez AJ, Starzl TE, Simmons RL, et al. CNS aspergillosis in organ transplantation: a clinicopathological study. *J Neurol Neurosurg Psychiatry* 1993;**56**:188—93.
34. Avet-Loiseau H, Mechinaud-Lacroix F, Cohen JY, Harousseau JL. Probable disseminated cerebral aspergillosis: recovery with medical treatment. *Nouv Rev Fr Hematol* 1994;**36**:419—22.
35. Coleman JM, Hogg GG, Rosenfeld JV, Waters KD. Invasive central nervous system aspergillosis: cure with liposomal amphotericin B, itraconazole, and radical surgery—case report and review of the literature. *Neurosurgery* 1995;**36**:858—63.
36. Wrzolek MA, Brudkowska J, Kozlowski PB, Rao C, Anzil AP, Klein EA, et al. Opportunistic infections of the central nervous system in children with HIV infection: report of 9 autopsy cases and review of the literature. *Clin Neuropathol* 1995;**14**:187—96.
37. Darras-Joly C, Veber B, Bedos JP, Gachot B, Regnier B, Wolff M. Nosocomial cerebral aspergillosis: a report of 3 cases. *Scand J Infect Dis* 1996;**28**:317—9.
38. Khoury H, Adkins D, Miller G, Goodnough L, Brown R, DiPersio J. Resolution of invasive central nervous system aspergillosis in a transplant recipient. *Bone Marrow Transplant* 1997;**20**:179—80.
39. Baslar Z, Soysal T, Hanci M, Aygun G, Ferhanoglu B, Sarioglu AC, et al. Successful outcome of *Aspergillus* brain abscess in a patient who underwent bone marrow transplantation for aplastic anemia. *Haematologia (Budap)* 1997;**28**:265—71.
40. Koh S, Ross LA, Gilles FH, Nelson MD, Mitchell WG. Myelopathy resulting from invasive aspergillosis. *Pediatr Neurol* 1998;**19**: 135—8.
41. Antunes NL, Hariharan S, DeAngelis LM. Brain abscesses in children with cancer. *Med Pediatr Oncol* 1998;**31**:19—21.
42. Viriyvejakul P, Phudhichareonrat S, Boonpasat Y, Viriyavejakul A, Rojanasunan P, Phophak N, et al. Intracerebral hemorrhage due to nosocomial aspergillosis following neurosurgery. *Southeast Asian J Trop Med Public Health* 1999;**30**:154—6.
43. Christophe C, Azzi N, Bouche B, Dan B, Levivier M, Ferster A. Magnetic resonance imaging and angiography in cerebral fungal vasculitis. *Neuropediatrics* 1999;**30**:218—20.
44. Abbasi S, Shenep JL, Hughes WT, Flynn PM. Aspergillosis in children with cancer: a 34-year experience. *Clin Infect Dis* 1999;**29**:1210—9.
45. Groll AH, Kurz M, Schneider W, Witt V, Schmidt H, Schneider M, et al. Five-year-survey of invasive aspergillosis in a paediatric cancer centre. Epidemiology, management and long-term survival. *Mycoses* 1999;**42**:431—42.
46. Ng A, Gadong N, Kelsey A, Denning DW, Leggate J, Eden OB. Successful treatment of *Aspergillus* brain abscess in a child with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2000;**17**:497—504.
47. de Medeiros BC, de Medeiros CR, Werner B, Neto JZ, Loddo G, Pasquini R, et al. Central nervous system infections following bone marrow transplantation: an autopsy report of 27 cases. *J Hematother Stem Cell Res* 2000;**9**:535—40.
48. Kleinschmidt-DeMasters BK. Central nervous system aspergillosis: a 20-year retrospective series. *Hum Pathol* 2002;**33**:116—24.
49. Saulsbury FT. Successful treatment of *Aspergillus* brain abscess with itraconazole and interferon-gamma in a patient with chronic granulomatous disease. *Clin Infect Dis* 2001;**32**:E137—9.
50. Auletta JJ, John CC. Spinal epidural abscesses in children: a 15-year experience and review of the literature. *Clin Infect Dis* 2001;**32**:9—16.
51. Rickert CH, Greiner C, Rellensmann G, Kehl HG, Scheld HH, Paulus W, et al. Mycotic cerebral vasculitis in a paediatric cardiac transplant patient excludes misadventure. *Int J Legal Med* 2002;**116**:233—7.
52. Psiachou-Leonard E, Sidi V, Tsivitanidou M, Gompakis N, Kolioukas D, Roilides E. Brain abscesses resulting from *Bacillus cereus* and an *Aspergillus*-like mold. *J Pediatr Hematol Oncol* 2002;**24**: 569—71.
53. Antony AK, Hong RW, Amieva M, Taekman MS, Huhn SL, Karanas YL. Free latissimus dorsi flap used in treatment of cerebral aspergillosis: a case report and review of the literature. *Microsurgery* 2003;**23**:313—6.
54. Okafuji T, Yabuuchi H, Nagatoshi Y, Hattanda Y, Fukuya T. CT and MR findings of brain aspergillosis. *Comput Med Imaging Graph* 2003;**27**:489—92.
55. Roilides E, Pavlidou E, Papadopoulos F, Panteliadis C, Farmaki E, Tamiolaki M, et al. Cerebral aspergillosis in an infant with corticosteroid-resistant nephrotic syndrome. *Pediatr Nephrol* 2003;**18**:450—3.
56. Baquero-Artigao F, Garcia-Miguel MJ, Hernandez F, Hernandez N, del Castillo F. Combined systemic and intrapleural treatment of *Aspergillus* pulmonary empyema after invasive aspergillosis. *Pediatr Infect Dis J* 2003;**22**:471—3.
57. Bethell D, Hall G, Goodman TR, Klein N, Pollard AJ. Resolution of orbitocerebral aspergillosis during combination treatment with voriconazole and amphotericin plus adjunctive cytokine therapy. *J Pediatr Hematol Oncol* 2004;**26**:304—7.

58. Alsultan A, Williams MS, Lubner S, Goldman FD. Chronic granulomatous disease presenting with disseminated intracranial aspergillosis. *Pediatr Blood Cancer* 2006;**47**:107—10.
59. Green M, Wald ER, Tzakis A, Todo S, Starzl TE. Aspergillosis of the CNS in a pediatric liver transplant recipient: case report and review. *Rev Infect Dis* 1991;**13**:653—7.
60. Groll AH, Jaeger G, Allendorf A, Herrmann G, Schloesser R, von Loewenich V. Invasive pulmonary aspergillosis in a critically ill neonate: case report and review of invasive aspergillosis during the first 3 months of life. *Clin Infect Dis* 1998;**27**: 437—52.
61. van Landeghem FK, Stiller B, Lehmann TN, Sarioglu N, Sander B, Lange PE, et al. Aqueductal stenosis and hydrocephalus in an infant due to *Aspergillus* infection. *Clin Neuropathol* 2000;**19**: 26—9.
62. Denning DW. Therapeutic outcome in invasive aspergillosis. *Clin Infect Dis* 1996;**23**:608—15.
63. Margolin JF, Steuber CP, Poplack DG. Acute lymphoblastic leukemia. In: Pizzo PA, Poplack DG, editors. *Principles and practice of pediatric oncology*. Fifth ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006. p. 538—90.
64. Walsh TJ, Roilides E, Cortez K, Kottilil S, Bailey J, Lyman CA. Control, immunoregulation, and expression of innate pulmonary host defenses against *Aspergillus fumigatus*. *Med Mycol* 2005;**43**: S165—72.
65. Boon AP, Adams DH, Buckels J, McMaster P. Cerebral aspergillosis in liver transplantation. *J Clin Pathol* 1990;**43**:114—8.
66. Denning DW, Marinus A, Cohen J, Spence D, Herbrecht R, Pagano L, et al. An EORTC multicentre prospective survey of invasive aspergillosis in haematological patients: diagnosis and therapeutic outcome. EORTC Invasive Fungal Infections Cooperative Group. *J Infect* 1998;**37**:173—80.
67. Ashdown BC, Tien RD, Felsberg GJ. Aspergillosis of the brain and paranasal sinuses in immunocompromised patients: CT and MR imaging findings. *Am J Roentgenol* 1994;**162**:155—9.
68. Herbrecht R, Letscher-Bru V, Oprea C, Lioure B, Waller J, Campos F, et al. *Aspergillus* galactomannan detection in the diagnosis of invasive aspergillosis in cancer patients. *J Clin Oncol* 2002;**20**: 1898—906.
69. Roilides E. Early diagnosis of invasive aspergillosis in small children. *Med Mycol* 2006;**44**(Suppl):199—205.
70. Viscoli C, Machetti M, Gazzola P, De Maria A, Paola D, Van Lint MT, et al. *Aspergillus* galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. *J Clin Microbiol* 2002;**40**:1496—9.
71. Starke JR, Mason EO, Kramer WG, Kaplan SL. Pharmacokinetics of amphotericin B in infants and children. *J Infect Dis* 1987;**155**: 766—74.
72. Hann IM, Prentice HG. Lipid-based amphotericin B: a review of the last 10 years of use. *Int J Antimicrob Agents* 2001;**17**:161—9.
73. Roilides E, Dotis J, Filioti J, Anaissie E. Systemic antifungal drugs: adjunctive antifungal therapy. In: Dismukes EW, Pappas GP, Sobel DJ, editors. *Clinical mycology*. New York: Oxford University Press; 2003. p. 125—39.