Clinical Neuropathology, Vol. 14, No. 4 – 1995 (187–196)

Opportunistic infections of the central nervous system in children with HIV infection: report of 9 autopsy cases and review of literature

M.A. Wrzolek[1,2], J. Brudkowska[2], P.B. Kozlowski[2], C. Rao[1], A.P. Anzil[1], E.A. Klein[3], C. Del Rosario[1], A. Abdu[1], L. Kaufman[4] and F.W. Chandler[5]

[1]*Department of Pathology, State University of New York Health Science Center, Brooklyn,* [2]*New York State Institute for Basic Research in Developmental Disabilities, Staten Island,* [3]*Department of Pathology, Staten Island University Hospital, Staten Island, NY,* [4]*Immunodiagnostic Laboratory, Emerging Bacterial and Mycotic Diseases Branch, National Center for Infectious Diseases, Atlanta, and* [5]*Department of Pathology, Medical College of Georgia, Augusta, GA, USA*

Abstract. Central nervous system (CNS) abnormalities attributed to direct effects of HIV infection are seen in most of children with acquired immunodeficiency syndrome (AIDS). Secondary CNS infections with opportunistic and common pathogens are infrequent in this age group. We report 9 cases of opportunistic infection of the CNS found among 65 autopsy cases of pediatric AIDS. These included 4 cases of cytomegalovirus (CMV) infection, 1 of which was associated with aspergillosis, and 2 cases of candidiasis, 1 of which coexisted with Mycobacterium avium intracellulare (MAI) infection. There were also 2 cases of leptomeningitis, 1 due to Mycobacterium tuberculosis (MTB) and the other to Cryptococcus neoformans. In 1 child progressive multifocal leukoencephalopathy (PML) coexisted with mycotic encephalitis caused by an Aspergillus sp.

Key words: AIDS – CNS – children – opportunistic infections

Introduction

Opportunistic infections of the CNS are common in adults with AIDS, encountered in up to 50% of cases in autopsy series [Gray et al. 1988]. The most frequent pathogens in adults include Toxoplasma gondii, Cryptococcus neoformans, and CMV, but a vast array of unusual pathogens have been reported. In contrast to adult AIDS patients, secondary CNS infection is infrequently seen in pediatric AIDS [Belman et al. 1988, Dickson et al. 1989, Kanzer 1990, Kozlowski et al. 1993].

Review of the autopsy files of the Neuropathology Laboratory of the Kings County Hospital Center at Brooklyn showed 65 cases of pediatric AIDS examined neuropathologically from 1981 to 1993. There were 35 females and 30 males. The age at death ranged from 3 months to 12 years. Only 2 children had been infected by transfusion of contaminated blood products; the remaining 63 were either documented or presumed to have had perinatal HIV infection. Nine of the children (14%) had opportunistic CNS infections and are the subject of this report. There were 4 cases of CMV infection, including 1 which coexisted with Aspergillus flavus infection. CNS involvement with Candida spp. was seen in 2 cases, 1 of which also had culture-proven MAI infection. In 1 case PML coexisted with a cerebral mycosis caused by an Aspergillus sp. There were 2 cases of leptomeningitis, 1 caused by C. neoformans and the other by MTB. Clinical and autopsy findings are summarized in Table 1.

Case reports

Case 1

A 10-month-old male with perinatal HIV infection had a history of repeated hospitalizations for pulmonary infections. Urine culture was positive for CMV at the age of 1 month. Two months before death he was admitted for seizures and pneumonia. A CT scan showed mass lesions in the left temporal lobe and the thalamic areas. CSF protein was 270 mg/dl, glucose 50 mg/dl, and microbiologic cultures were negative.

At autopsy the brain weighed 860 g (normal for age = 810 g). Multiple bilateral firm yellowish areas, some with hyperemic rims, 0.2 – 3 cm in diameter, were seen in the

Received April 13, 1994.

Correspondence to Dr. M.A. Wrzolek, SUNY HSCB, Department of Pathology, Box 25, 450 Clarkson Avenue, USA-Brooklyn, N.Y. 11203, USA.

Table 1 Demographic information and autopsy findings in 9 children with secondary CNS infection

Case	Age, sex	CNS infection	Other CNS findings	General autopsy infections
1	10 months, male	CMV	primary CNS lymphoma	CMV pneumonia
2	26 months, female	CMV	microencephaly, HIV encephalitis	oral candidiasis, disseminated CMV infection
3	5 months male	CMV	basal ganglia and white matter mineralization	oral candidiasis, disseminated CMV infection, PCP
4	20 months male	CMV, Aspergillus flavus	diffuse white matter pallor and astrocytosis	Candida esophagitis, disseminated CMV infection
5	66 months, female	M. tuberculosis	microencephaly	disseminated tuberculosis with multiple abscesses
6	72 months, female	Candida sp., MAI	microencephaly, HIV encephalitis	disseminated candidiasis, disseminated MAI infection
7	42 months, female	Candida sp.	microencephaly, white matter pallor, cortico-spinal tract degeneration	no evidence of systemic infection
8	12 years, male	Aspergillus sp., JC virus (PML)	none	pulmonary aspergillosis, Candida esophagitis
9	6 years, male	Cryptococcus neoformans	primary CNS lymphoma	disseminated cryptococcosis, PCP, CMV adrenalitis

basal ganglia and thalami, cerebral cortex, and the white matter.

Microscopic examination revealed multiple foci of malignant B cell lymphoma, mixed small and large cell type, involving brain parenchyma and leptomeninges. In addition, there was extensive ependymitis and subependymitis with numerous cytomegalic cells (Figure 1). Similar changes were present focally in the subpial regions of the cerebral hemispheres and the brain stem and involved 1 of the oculomotor nerves. Scattered microglial nodules, without multinucleated giant cells (MGC) or cytomegalic cells, were seen throughout the CNS, often contiguous to the subpial and subependymal inflammatory lesions.

The general autopsy showed CMV pneumonitis, bronchopneumonia with microabscesses, and bilateral pyothoraces. There were generalized lymphadenopathy and splenomegaly with lymphoid depletion but no evidence of extra-CNS lymphoma.

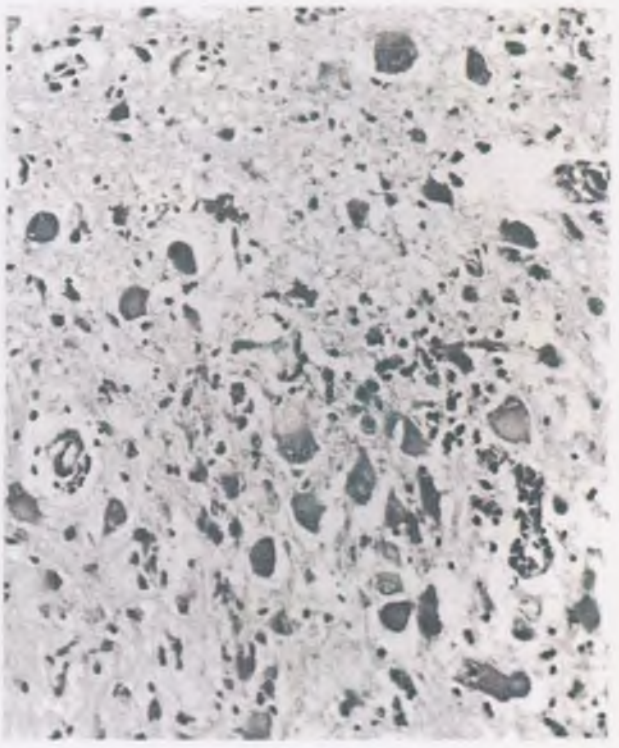


Fig. 1 Case 1: CMV encephalitis; subependymal area of necrotizing inflammation contains several inclusion-bearing cytomegalic cells (HE).

Case 2

A 26-month-old female with perinatal HIV infection developed normally up to 1 year of age when she began to lose neurodevelopmental skills. She was admitted 10 days before death with fever, hematemesis, seizures, athetoid movements, and decerebrate posturing. CSF was clear, with no cells. Smears, test for cryptococcal antigen, and bacterial, mycobacterial and viral cultures of the CSF were negative.

At autopsy the brain weighed 689 g (normal for age = 1,100 g), with reduced volume of the white matter and triventricular dilatation. No abnormalities of the ventricular lining were detected on gross examination.

Microscopic examination revealed extensive necrotizing encephalomyelitis with numerous cytomegalic cells. The lesions were predominantly subependymal, involving all 4 ventricles and the aqueduct and subpial, involving the brain stem and cervical segments of the spinal cord. In addition, there were features of HIV-encephalitis (HIVE) and multiple foci of mineralization were seen in the basal ganglia. General autopsy findings included disseminated CMV infection.

Case 3

A 5-month-old male with perinatal HIV infection had a history of failure to thrive and a hospital admission at 3

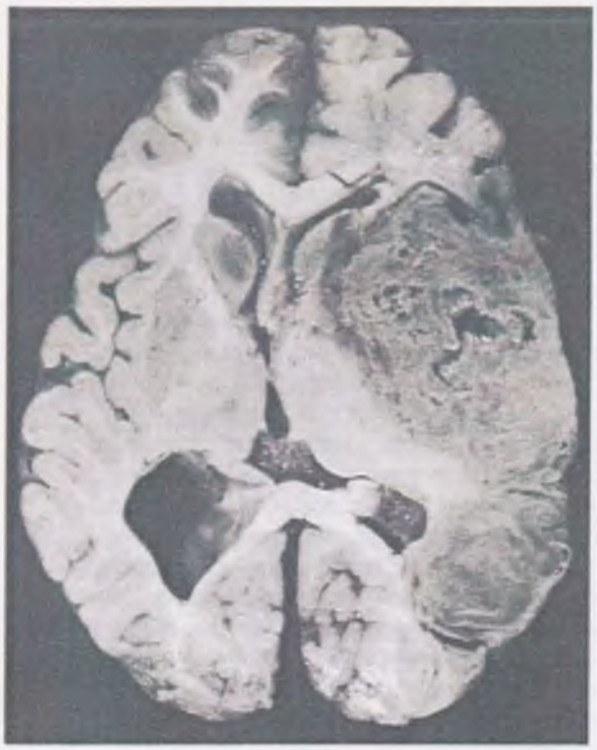


Fig. 2a

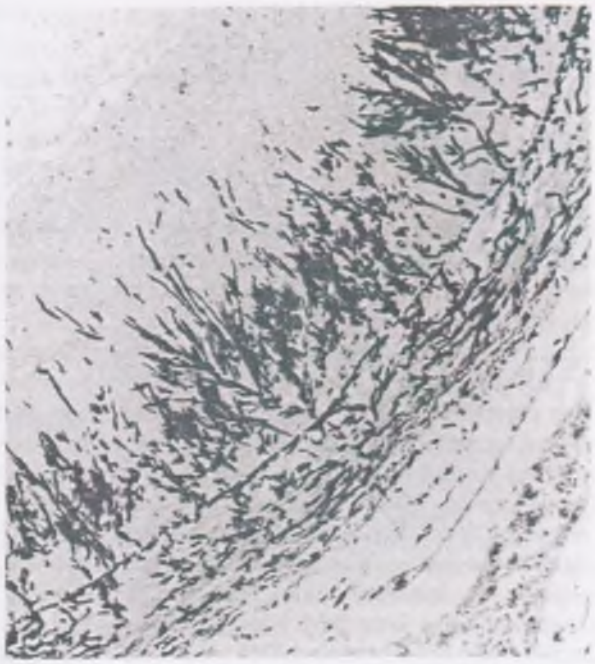


Fig. 2b

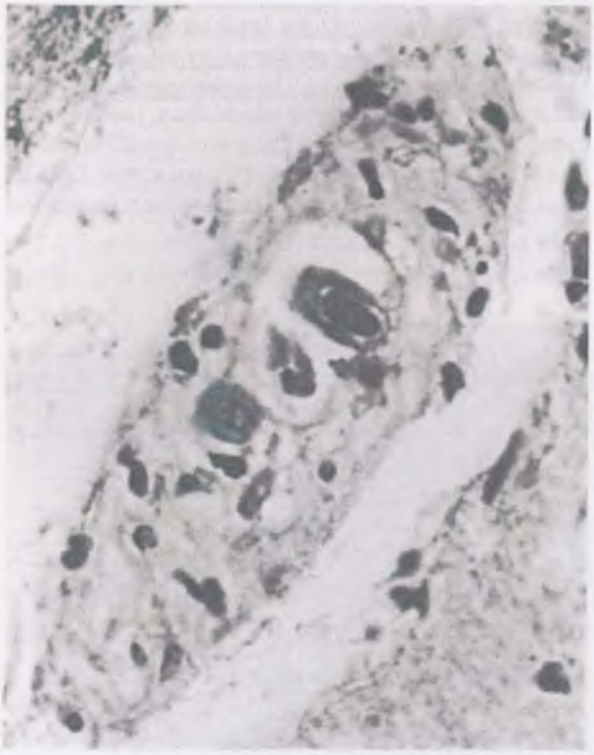


Fig. 2c

Fig. 2a–c Case 4: a) Horizontal section of brain with huge necrotic mass within right hemisphere; b) dichotomously branched hyphae of Aspergillus sp. infiltrating wall of large artery (GMS); c) CMV-infected endothelial cell of small blood vessel at periphery of necrotic lesion (HE)

months of age for fever, diarrhea and suspected sepsis. One month before death he was hospitalized with bilateral pneumonia and diarrhea. Neurologic examination showed generalized hypertonicity. CSF examination showed 2 WBC/cu mm, protein of 37 mg/dl, and glucose of 94 mg/dl (serum glucose 138 mg/dl). Urine and nasopharyngeal cultures were positive for CMV.

At autopsy the brain weighed 620 g (normal for age = 644 g). There was subacute nodular encephalitis with multiple disseminated microglial nodules, 1 of which contained a single cytomegalic cell. No MGC were seen. Microscopic foci of necrosis were noted in the basal ganglia and pons. Extensive perivascular and interstitial mineralization was present in the basal ganglia and central white matter. General autopsy revealed disseminated CMV infection and Pneumocystis carinii pneumonia (PCP).

Case 4

A 20-month-old male with perinatal HIV infection had recurrent bouts of pneumonia and septicemia and a history of cardiopulmonary arrest as well as transient pancytopenia at 16 months of age. He had also been diagnosed with CMV chorioretinitis. At that time a CT scan showed atrophy of the brain but no focal lesions. On final admission for fever and seizures at 18 months of age he was lethargic and quadriplegic, and hypertonic with increased deep tendon reflexes. CSF was clear with no WBC, protein of 37

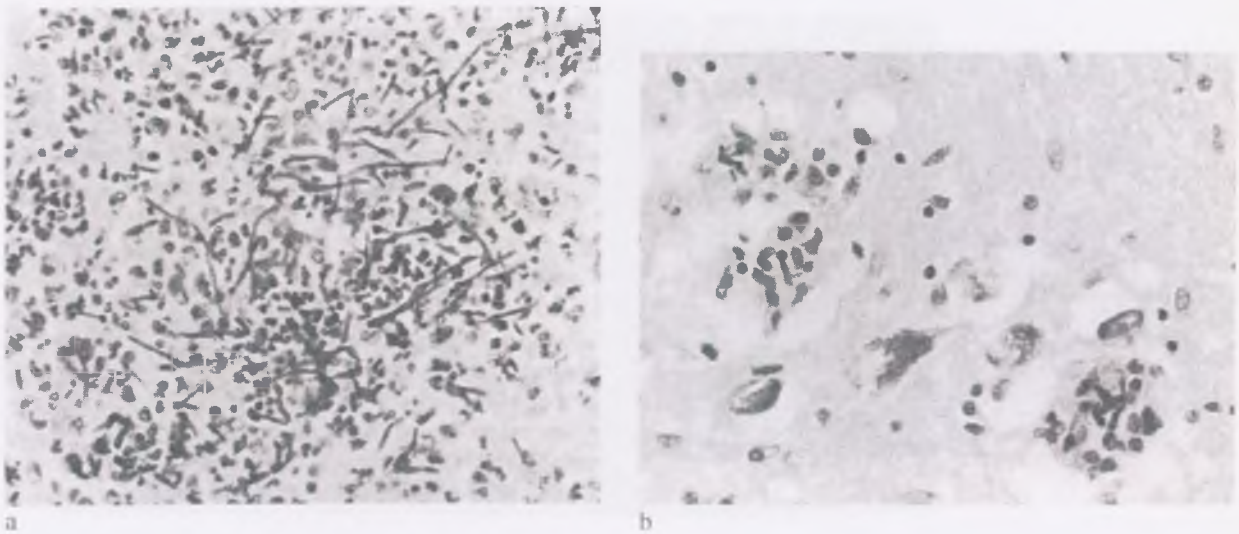
mg/dl, and glucose of 95 mg/dl (serum glucose 140 mg/dl). One month later a 4 cm area of swelling was noted over the right temporal region. A CT scan showed hyperattenuation in the right temporal and parietal lobes with areas of mixed attenuation and surrounding edema. There was marked shift to the left with compression of the right and dilatation of the left lateral ventricle. An overlying bony defect with soft tissue swelling was also evident. An aspirate of the soft tissue swelling grew Aspergillus flavus. The patient did not respond to Amphotericin B and expired at the age of 20 months.

At autopsy the brain weighed 725 g (normal for age = 1,050 g). A huge necrotic mass measuring 9 × 8 × 5 cm was present in the right cerebral hemisphere from the frontal to the occipital lobes (Figure 2a). The mass extended through the dura and the temporal bone into subcutaneous tissue. There was a small area of infarction of preserved brain tissue in the parietooccipital region, adjacent to the necrotic mass. The right lateral ventricle was compressed. Ipsilateral uncal herniation was present. Microscopically there were numerous hyaline dichotomously branched, septate hyphae characteristic of an Aspergillus sp. within the amorphous necrotic mass. At the periphery of the mass the fungi were seen within the walls of the leptomeningeal vessels and large arteries of the circle of Willis (Figure 2b). Evidence of CMV infection was also present with focal ependymitis and involvement of small parenchymal blood vessels at the periphery of the necrotic mass (Figure 2c). There were no features of HIVE, but the central white matter of the left hemisphere and the corticospinal tracts (CST) at the level of the medulla and the spinal cord showed diffuse myelin pallor with astrocytosis. Evidence of systemic aspergillosis was not seen at general autopsy, except for involvement of the cranium and soft tissues of the head. There were disseminated CMV infection, pulmonary and renal staphylococcal abscesses, subacute mitral endocarditis, and Candida esophagitis.

Case 5

A 5-year-old female, born of HIV-positive parents and previously hospitalized for lymphadenopathy and pneumonia, was readmitted to the hospital with low grade fever and bilateral rales. Her father was known to have drug-resistant MTB infection. Sputum cultures were positive for MTB, resistant to INH and Rifampin (identical to the organisms isolated from her father). Her condition deteriorated despite extensive antituberculous therapy, with clinical evidence of CNS involvement, with withdrawal, increased deep tendon reflexes, and clonus in the lower extremities.

At autopsy the brain weighed 780 g (normal = 1,150 g) and appeared atrophic. Several circumscribed foci of yellowish-green exudate were noted in the subarachnoid space over the convexities, extending to involve superficial cortex and measuring up to 1.5 cm in diameter. Microscopic examination revealed foci of severe but circumscribed leptomeningitis, with a mixture of suppurative and mononuclear inflammatory infiltrate. Inflammation involved the walls of the leptomeningeal blood vessels and extended superficially into the brain parenchyma (Figure 3). Focal necrosis of the inflammatory infiltrate and the vascular walls was noted. Granulomas, epithelioid cells, and MGC were not seen. A Ziehl-Neelsen stain revealed numerous acid-fast bacilli (AFB) within the inflammatory foci. There was no evidence of HIV-associated CNS lesions. General autopsy showed multiple abscesses teaming



a b

Fig. 3 Case 5: a) Multiple yeast forms and pseudohyphae of a Candida sp. within cortical microabscess (PAS); b) fungi within multinucleated giant cells of microglial nodule (PAS).

with mycobacteria in all internal organs, soft tissues and bones.

Case 6

A 6-year-old female, whose parents were HIV-positive, developed normally until 22 months prior to her death, when she was hospitalized for lymphocytic interstitial pneumonitis and weight loss. Developmental regression was noticed, accompanied by muscular spasticity, slurred speech, and focal seizures. Later, she was hospitalized for whooping cough and diarrhea due to MAI infection. During terminal hospitalization she received antibiotic therapy for pneumonia and staphylococcal sepsis.

At autopsy the brain weighted 856 g (normal for age = 1,243 g) and appeared atrophic. Microscopic examination revealed multiple microabscesses (Figure 3a) and microglial nodules (Figure 3b) throughout the CNS that contained budding yeasts and pseudohyphae morphologically consistent with those of a Candida sp. In the microglial nodules the fungi were seen within MGC. Basal ganglia showed extensive perivascular and parenchymal mineralization. Moderate to severe gliosis was present in the CST in the brain stem and spinal cord. Special stains for AFB revealed a few small collections of macrophages with phagocytized mycobacteria in the choroid plexus. General autopsy revealed disseminated MAI infection, chronic esophagitis with ectasia and ulcers due to a Candida infection, and disseminated candidiasis.

Case 7

A 3-and-a-half-year-old female with perinatal HIV infection and several hospital admissions for respiratory tract infections, had Burkitt's lymphoma of the anterior mediastinum, treated with surgery and chemotherapy. She went into remission, but had dramatic weight loss and was readmitted to implement total parenteral nutrition (TPN). The hospital course was complicated by cardiac and renal failure, anemia, and thrombocytopenia with gastrointestinal bleeding. She developed C. albicans sepsis, was treated with Amphotericin B, but died on the 54th hospital day.

At autopsy the brain weighed 785 g (expected for age = 1,149 g) and appeared atrophic. Microscopic examination revealed sparse isolated microglial nodules with MGC and a single granuloma in the spinal leptomeninges. The PAS stain revealed fungal forms consistent with a Candida sp. within the MGC. In addition, there were focal gliosis of the hemispheric white matter and bilateral CST degeneration. General autopsy showed malignant lymphoma involving lymph nodes, liver and spleen. There was no evidence of opportunistic infections outside the CNS.

Case 8

A 12-year-old male with perinatal HIV infection and a history of testicular lymphoma treated with chemotherapy, complicated by severe pancytopenia, developed neurological signs and symptoms a few days before death.

At autopsy the brain weighed 1,300 g and appeared swollen. A large hemorrhagic area of necrosis was present within the right basal ganglia, thalamus and the central white matter, extending through the corpus callosum into the left hemisphere. An area of granularity and softening was seen within the cerebellar white matter. Microscopically there were numerous hyaline hyphae within necrotic foci with marked hyphal angioinvasion and little or no inflammatory reaction (Figure 5a). The septate hyphae measured 3 – 6 μm in width and showed predominantly

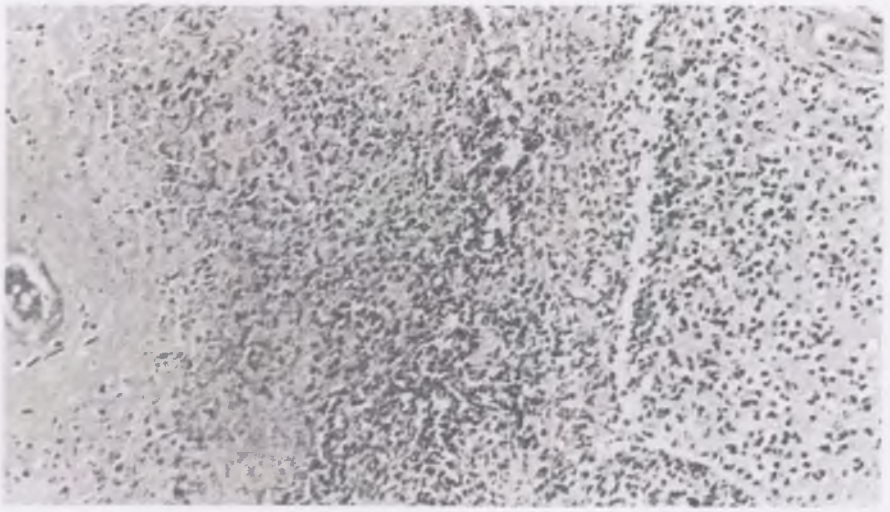


Fig. 4 Case 6: Suppurative inflammation in the leptomeninges extends into cerebral cortex in a case of Mycobacterium tuberculosis infection; note necrotic leptomeningeal blood vessel (HE).

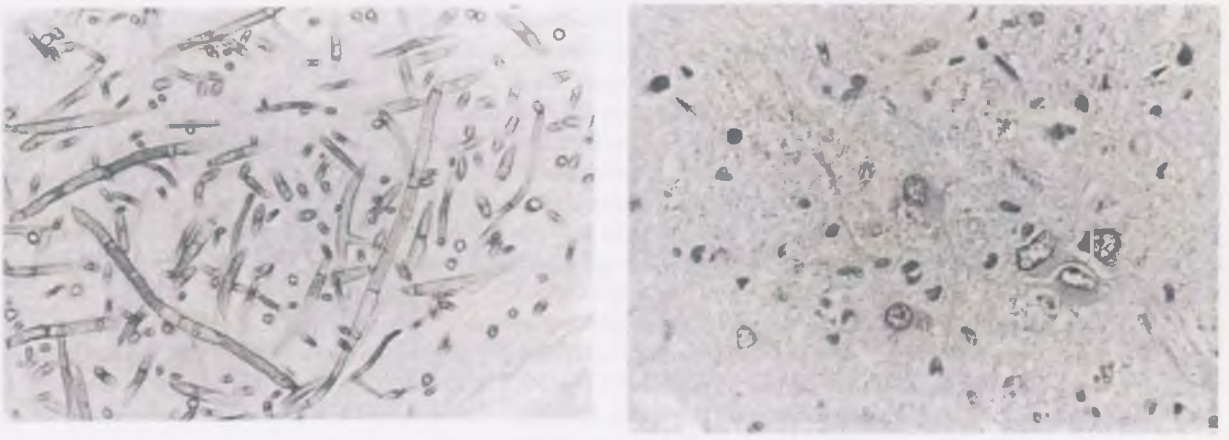


Fig. 5 Case 8: a) Aspergillus sp. hyphae within cerebral blood vessel; note septae and atypical right angle branching (GMS); b) demyelinated lesion of PML with inclusion-bearing oligodendrocytes (arrows) and bizarre astrocytes (HE).

right angle, nonprogressive branching. The width of the branched hyphae tended to be less than the parents' ones, and constriction was often seen at the site of branching. Yeast forms were not seen. These morphologic features were suggestive of a Fusarium sp. However, the hyphae were negative when stained with fluorescein sothiocyanate-conjugated rabbit anti-F. solani globulin, while strongly positive when stained with conjugated A. fumigatus antiglobulin [Kaufman 1992]. The cerebellar lesion showed features of PML, with demyelination, bizarre astrocytes and inclusion-bearing oligodendrocytes (Figure 5b). Multiple small foci of PML were also seen in the brain stem. General autopsy revealed pulmonary aspergillosis and Candida esophagitis.

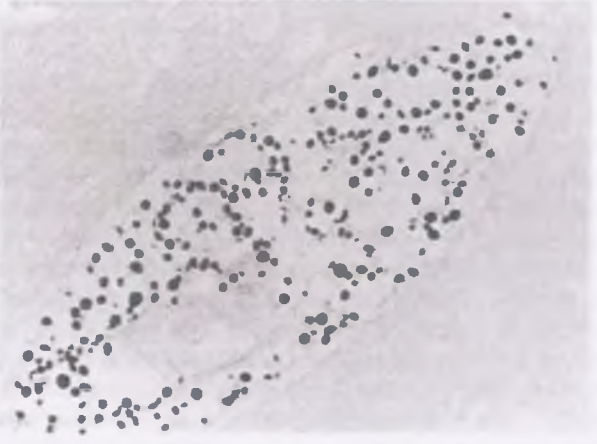


Fig. 6 Case 9: Multiple budding cryptococci within Virchow-Robin space in cerebral cortex; note the narrow-based budding (GMS).

Case 9

A 6-year-old male with perinatal HIV infection was brought unresponsive to the hospital and died in the emergency room.

The brain weighed 1,180 g and showed no gross abnormalities. Microscopically there was a diffuse cryptococcal leptomeningitis characterized by numerous predominantly extracellular yeast forms with prominent mucin-positive capsules within the subarachnoid space and, focally, in the Virchow-Robin spaces (Figure 6). There was virtually no inflammatory reaction. A small focus of lymphoma (B-cell, small cell type) was seen in the left caudate nucleus. HIV-associated lesions were not seen. General autopsy revealed disseminated cryptococcosis, PCP, and CMV adrenalitis.

Discussion

Secondary infections of the CNS are frequently seen in adults with AIDS but are rare in HIV-infected children. These infections occurred in 14% of pediatric cases in the present series, and from 0 – 14% in other series of pediatric AIDS [Belman et al. 1988, Dickson et al. 1989, Kanzer 1990, Kozlowski et al. 1990, 1993].

In our series CNS involvement resulted from disseminated infection by the respective pathogen, except for 1 case of an apparently isolated Aspergillus infection of the CNS. Comparison with the results of general autopsy in the same pediatric AIDS series indicated that the CNS was involved in only a minority of children with systemic infections (Table 2). Usually, secondary CNS infection is not clinically recognized in terminally ill children, who often show severe neurodevelopmental symptoms of progressive HIV encephalopathy. In addition to lower pre-

Table 2 Incidence of opportunistic infections in 65 children with AIDS

Pathogen	General autopsy	Central nervous system
Candida sp.	35	2
Pneumocystis carinii	14	–
Cytomegalovirus	11	4
M. avium-intracellulare	10	1
Herpes simplex virus	4	–
M. tuberculosis	3	1
Cryptosporidium sp.	2	–
Cryptococcus neoformans	2	1
Aspergillus sp.	2	2

valence of secondary CNS infections in children with AIDS, the pathogens most commonly affecting children are different from those in adults.

Toxoplasma gondii, the leading cause of secondary CNS infection in adult AIDS patients, is extremely rare in pediatric AIDS. There are single case reports of CNS toxoplasmosis in children with HIV infection [Biggemann et al. 1987, Cohen-Addad et al. 1988, Miller et al. 1991, Mitchell et al. 1990, Scott et al. 1985, Shanks et al. 1987, Wahn et al. 1986]. In most cases the clinical presentation was similar to non-AIDS children with congenital toxoplasmosis, i.e. at birth or during the first months of life, with hepatosplenomegaly, chorioretinitis, seizures and other neurologic signs. When available, the neuropathologic findings were also suggestive of congenital toxoplasmosis. Two children, both 5 years old at the time of death, who acquired HIV infection from blood transfusion and from an infected sibling, respectively, had clinical courses similar to adult patients with CNS toxoplasmosis [Biggemann et al. 1987, Wahn et al. 1986]. The source of toxoplasma infection in these 2 children was not established. Neuropathologic findings of multiple necrotizing granulomas in 1 of these children were identical to those most frequently reported in adult AIDS patients [Biggemann et al. 1987].

Almost all cases of congenital toxoplasmosis result from primary maternal infection during the pregnancy. Rare cases of transmission during the latent stage of toxoplasmosis during pregnancy have been reported in immunocompromised women [Remington et al. 1990]. It is not clear if and to what extent maternal HIV-infection and the resulting immunodeficiency modify the intrauterine transmission of toxoplasma infection. However, the rarity of toxoplasmosis in children with perinatal HIV infection suggests that the rate or mode of intrauterine transmission of toxoplasma infection is not dramatically altered.

CMV, the most common secondary viral pathogen affecting the CNS in adult AIDS, is also the most frequent cause of secondary CNS infection in pediatric AIDS. It was seen in 4 cases (6.2%) in our series. The relative frequency of CMV infection in children with AIDS may be related to the common and early occurrence of CMV infection in the general population. Approximately 1% of all neonates are infected with CMV in utero, and from 36 – 56% of infants become infected during the first year of life [Ho 1990]. It is not presently known if maternal HIV infection increases the risk of congenital or perinatal CMV infection in their offspring. Clinical evidence of congenital CMV infection of the CNS with primary microcephaly and periventricular calcifications at birth is exceptional in HIV-infected neonates [Belec et al. 1990, Curless et al. 1987]. More commonly, CNS lesions caused by CMV in HIV-infected children are not different from those encountered in adult AIDS patients [Vinters et al. 1989], except for CMV polyradiculoneuritis, which has been documented only in adults. Extensive necrotizing encephalomyelitis, with subependymal and subpial distribution of the lesions was seen in 2 of the 4 cases of CMV infection in the present series; 1 case had disseminated nodular encephalitis, and 1 had focal CMV vasculitis at the periphery of a large aspergillus lesion. Typical cytomegalic inclusion-bearing cells may be scanty or altogether absent in cases of nodular encephalitis and CMV infection may coexist with HIVE. Because these conditions resemble each other histopathologically, and because special studies to detect CMV genome and/or antigens in the present series were not done, it is possible that CMV infection of the CNS was not detected in some of the cases.

Other pathogens of the herpes virus group have been infrequently documented as a cause of CNS pathology in children with AIDS. An unusual form of vasculopathy involving the circle of Willis has been reported in a child with prolonged cutaneous varicella zoster virus (VZV) infection, and has been attributed to VZV [Frank et al. 1989]. One case of probable CNS involvement in the course of disseminated VZV infection is listed in a report on 8 HIV-infected children with primary VZV infection [Jura et al. 1989].

Chronic, recurrent or disseminated herpes simplex virus (HSV) infections are listed as indicator diseases in the CDC case criteria for pediatric AIDS [CDC 1987]. However, disseminated infection with HSV is relatively rare in children with AIDS [Bryson et al. 1991] and we are not aware of well-documented cases of CNS involvement.

Epstein-Barr virus (EBV) has been implicated as a causative agent in the development of lymphoproliferative disorders and lymphomas, including primary CNS lymphomas, in AIDS. The EBV genome has been found in a high percentage of primary CNS lymphomas in adults with AIDS [Morgello 1992]. A few case studies have also identified the EBV genome in childhood AIDS-related CNS lymphomas [Del Mistro et al. 1990].

PML due to JC virus has been reported in 4% of autopsied adult AIDS cases. In the immunocompetent host primary infection with JC virus is asymptomatic and it

occurs most commonly during childhood or adolescence. PML occurs almost exclusively in profoundly immunocompromised hosts as a result of reactivation of latent infection. In AIDS PML is seen predominantly in those over 50 years of age, or in those, irrespective of age, who acquired HIV infection by blood transfusion [Holman et al. 1991]. Isolated cases of PML in children with AIDS have been reported [Berger et al. 1992, Dozic et al. 1990, Lang et al. 1992, Singer et al. 1993, Vandersteenhoven et al. 1992]. Only 12 children with PML and HIV infection had been reported to the CDC as of 1990 [Holman et al. 1991]. PML was most often seen in older HIV-infected children, the youngest was 7 years old [Vandersteenhoven et al. 1992]. The only case of PML in our series was seen in a 12-year-old boy with HIV infection acquired by blood transfusion in the neonatal period – the oldest patient in this series.

Fungal infections, with the exception of mucosal candidiasis, are infrequent in children with AIDS. Disseminated mycoses usually occur in the presence of additional predisposing conditions, such as neutropenia, indwelling catheters, broad-spectrum antibiotics, or abdominal surgery [Walsh et al. 1991]. Candidiasis in children with AIDS follows the pattern seen in adult patients: although the majority of patients have mucosal candidiasis, invasive and disseminated disease are rare [Walsh et al. 1991]. Two children in the present series had CNS candidiasis, both in the course of terminal disseminated infection. In 1 case disseminated candidiasis occurred in the course of TPN in a child who received chemotherapy for Burkitt's lymphoma. The other child was treated with broad-spectrum antibiotics for staphylococcal sepsis.

Aspergillus spp. are ubiquitous fungi that only rarely cause disease in AIDS patients. Indeed, invasive aspergillosis has been removed from the original CDC list of opportunistic infections indicative of AIDS. The 2 children with CNS aspergillosis in the present series, are, to our knowledge, the only pediatric AIDS cases documented to have such infections. In 1 case a huge necrotic mass was found in the cerebral hemisphere extending into the bone and soft tissues of the head. No extracerebral focus of aspergillosis was identified at autopsy, and the source of the infection is speculative. It is unclear whether the transient granulocytopenia seen a few months before death contributed to the development of aspergillus infection. In the other child aspergillosis developed in the setting of chemotherapy-induced pancytopenia and pulmonary involvement was seen at autopsy.

Cryptococcal meningitis is the leading form of CNS fungal infection in adult AIDS, occurring in 6 – 13% of patients. However, only isolated cases have been reported in children and adolescents with AIDS [Dozic et al. 1990, Leggiardo et al. 1991, Pippard et al. 1986, Rubin et al. 1989, Ting et al. 1991]. Although cryptococcal meningitis has been documented in a 4-year-old child with perinatal HIV infection [Leggiardo et al. 1991], children with this complication generally tend to be older and infected by HIV-contaminated blood products [Dozic et al. 1990, Leggiardo et al. 1991, Pippard et al. 1986, Rubin et al. 1989, Ting et al. 1991]. In our series the only child with cryptococcal meningitis had perinatal HIV infection and died at the age of 6 with widely disseminated cryptococcosis.

Histoplasma var. capsulatum and Coccidioides immitis affect adult AIDS patients in endemic areas but have not been reported in pediatric AIDS.

Tuberculosis has recently emerged as a common complication of adult AIDS. It is anticipated that the trends observed among adults with AIDS will soon be followed by the pediatric age group [Braun et al. 1992, Husson 1991]. The only child in our series with CNS tuberculosis had circumscribed purulent leptomeningitis teaming with mycobacteria. This unusual pattern of a suppurative reaction to MTB has been observed in several adult AIDS patients with CNS tuberculosis [Anzil et al. 1992].

Microorganisms of the MAI complex are a frequent cause of systemic infection in AIDS. However, MAI infection of the CNS is a rare incidental finding associated with other focal CNS lesions [Anders et al. 1986]. In 1 child with systemic MAI infection AFB were seen within reactive macrophages adjacent to the area of infarction [Dickson et al. 1989]. There was only 1 case of MAI infection of the CNS in the present series, even though a total of 10 cases of disseminated infection were documented. As an incidental finding, AFB were seen within macrophages in the choroid plexus in this case.

Multiple or recurrent serious bacterial infections are included in the CDC case criteria of pediatric AIDS [CDC 1987]. Clinically bacterial meningitis is relatively infrequent. It was seen in 1 of 372 HIV-infected children in a study of intravenous immune globulin prophylaxis [The National Institute of Child Health 1991]. In the present autopsy series there was only 1 case of focal purulent leptomeningitis, presumably due to Enterococcus faecalis.

The reason for different frequency of secondary CNS infections between children and adults with AIDS is unclear. The most prevalent secondary CNS infections seen in adults, such as toxoplasmosis, CMV infection and PML, usually result from reactivation of latent or persistent infection and not from primary exposure to these pathogens. It has been suggested that young children with AIDS may not yet be exposed to certain pathogens that commonly affect adult AIDS patients [Kanzer 1990]. Pediatric AIDS epidemics, as a natural consequence of HIV infection spreading in young female populations, lags behind the epidemics in adults. Because most children with congenital HIV infection die in infancy we have only recently begun to observe the longer-surviving children with perinatal HIV infection. A more adult-like pattern of secondary CNS infections may emerge in these children exposed to a variety of pathogens, including those affecting their immunocompromised parents. As illustrated by the child in our series who acquired tuberculosis from her

father, the changing patterns of secondary infections in the adult AIDS population may have an impact on pediatric AIDS patients.

Analysis of case reports of children whose opportunistic infections of the CNS resemble those seen in adults suggests that the "adult" pattern of CNS infections tends to occur in older children and adolescents, and often in those who acquired HIV infection postnatally by the blood transfusion. Infection with some fungal pathogens appears to be related to additional risk factors, and not specifically to HIV-induced immunosuppression.

Acknoledgement

Supported in part by NIH Grant HD24884.

REFERENCES

Anders KH, Guerra WF, Tomiyasu U, Verity MA, Vinters HV 1986 The neuropathology of AIDS. UCLA experience and review. Am J Pathol *124:* 537-558

Anzil AP, Rao C, Seymour AW, Sher JH 1992 CNS tuberculosis in AIDS: a synopsis of 6 cases with emphasis on morphology. J Neuropathol Exp Neurol *51:* 375

Belec L, Tayot J, Tron P, Mikol J, Scaravilli F, Gray F 1990 Cytomegalovirus encephalopathy in an infant with congenital acquired immuno-deficiency syndrome. Neuropediatrics *21:* 124-129

Belman AL, Diamond G, Dickson D, Horoupian D, Llena J, Lantos G, Rubinstein A 1988 Pediatric acquired immunodeficiency syndrome. Neurologic syndromes. AJDC *142:* 29-35

Berger JR, Scott G, Albrecht J, Belman AL, Tornatore C, Major EO 1992 Progressive multifocal leukoencephalopathy in HIV-1-infected children. AIDS *6:* 837-841

Biggemann B, Voit T, Neuen E, Wechsler W, Kramer H, Kries von R, Wahn V 1987 Neurological manifestations in three German children with AIDS. Neuropediatrics *18:* 99-106

Braun MM, Cauthen G 1992 Relationship of the human immunodeficiency virus epidemic to pediatric tuberculosis and bacillus Calmette-Guérin immunization. Pediatr Infect Dis J *11:* 220-227

Bryson Y, Arvin A 1991 Herpes group virus infections in HIV-1-infected infants, children, and adolescents. In: *Pizzo PA, Wilfert CM (eds)* Pediatric AIDS; the challenge of HIV infection in infants, children, and adolescents. Williams and Wilkins, Baltimore, pp 245-265

CDC 1987 Classification system for human immunodeficiency virus (HIV) infection in children under 13 years of age. MMWR *36:* 225-236

Cohen-Addad NE, Joshi VV, Sharer LR, Epstein LG, Gubitosi TA, Oleske JM 1988 Congenital acquired immunodeficiency syndrome and congenital toxoplasmosis: pathologic support for a chronology of events. J Perinatol *8:* 328-331

Curless RG, Scott GB, Post MJ, Gregorios JB 1987 Progressive cytomegalovirus encephalopathy following congenital infection in an infant with acquired immunodeficiency syndrome. Childs Nerv Syst *3:* 255-257

Del Mistro A, Laverda A, Calabrese F, De Martino M, Calabri G, Cogo P, Cocchi P, D'Andrea E, De Rossi A, Giaquinto C, Giordano R, Nieri RM, Salvi G, Pennelli N, Chieco-Bianchi L 1990 Primary lymphoma of the central nervous system in two children with acquired immune deficiency syndrome. Am J Clin Pathol *94:* 722-728

Dickson DW, Belman AL, Park YD, Wiley C, Horoupian DS, Llena J, Kure K, Lyman WD, Morecki R, Mitsudo S, Cho S 1989 Central nervous system pathology in pediatric AIDS: An autopsy study. APMIS *Suppl 8:* 40-57

Dozic S, Suvakovic V, Cvetkovic D, Jevtovic D, Skender M 1990 Neoplastic angioendotheliomatosis (NAE) of the CNS in a patient with AIDS subacute encephalitis, diffuse leukoencephalopathy and meningo-cerebral cryptococcosis. Clin Neuropathol *9:* 284-289

Frank Y, Lun W, Kahn E, Farmer P, Gorev M, Pahwa S 1989 Multiple ischemic infarcts in a child with AIDS, Varicella zoster infection, and cerebral vasculitis. Pediatr Neurol *5:* 64-67

Gray F, Gherardi R, Scaravilli F 1988 The neuropathology of the acquired immune deficiency syndrome (AIDS). A review. Brain *111:* 245-266

Ho M 1990 Epidemiology of cytomegalovirus infections. Rev Infect Dis 12 *Suppl 7:* S701-S710

Holman RC, Janssen RS, Buehler JW, Zelasky MT, Hooper WC 1991 Epidemiology of progressive multifocal leukoencephalopathy in the United States: analysis of national mortality and AIDS surveillance data. Neurology *41:* 1733-1736

Husson RN 1991 Mycobacterial infections. In: *Pizzo PA, Wilfert CM (eds)* Pediatric AIDS: The Challenge of HIV Infection in Infants, Children, and Adolescents. Williams and Wilkins, Baltimore, pp 209-224

Jura E, Chadwick EG, Josephs SH, Steinberg SP, Yogev R, Gershon AA, Krasinski KM, Borkowsky W 1989 Varicella-zoster virus infection in children infected with human immunodeficiency virus. Pediatr Infect Dis J *8:* 586-590

Kanzer MD 1990 Opportunistic central nervous system infections in pediatric AIDS and review of the cases from the registry of the Armed Forces Institute of Pathology. In: *Kozlowski PB, Snider DA, Vietze PM, Wisniewski HM (eds)* Brain in pediatric AIDS. Karger, Basel, pp 165-169

Kaufman L 1992 Immunohistologic diagnosis of systemic mycoses: An update. Eur J Epidemiol *8:* 377-382

Kozlowski PB, Sher JH, Dickson DW, Llena JF, Sharer LR, Cho ES, Kanzer MD 1990 Central nervous system in pediatric HIV infection: A multicenter study. In: MKozlowski PB, Snider DA, Vietze PM, Wisniewski HM (eds) Brain in pediatric AIDS. Karger, Basel, pp 132-146

Kozlowski PB, Anzil PA, Rao C, Sharer L, Cho ES, Dickson DW, Weidenheim KM, Llena JF, Nelson SJ, Kanzer MD, Burns D 1993 Central nervous system (CNS) in children with AIDS – a multicenter study of 174 cases. Clin Neuropathol *12:* S25

Lang C, Jacobi G, Kreuz W, Hacker H, Herrmann G, Keul HG, Thomas E 1992 Rapid development of giant aneurysm at the base of the brain in an 8-year-old boy with perinatal HIV infection. Acta Histochem *Suppl XLII:* 83-90

Leggiardo RJ, Kline MW, Hughes WT 1991 Extrapulmonary cryptococcosis in children with acquired immunodeficiency syndrome. Pediatr Infect Dis J *10:* 658-662

Miller MJ, Remington JS 1991 Toxoplasmosis in infants and children with HIV infection or AIDS. In: *Pizzo PA, Wilfert CM (eds)* Pediatric AIDS. The Challenge of HIV Infection in Infants, Children and Adolescents. Williams and Wilkins, Baltimore, pp 299-307

Mitchell CD, Erlich SS, Mastrucci MT, Hutto SC, Parks WP, Scott GB 1990 Congenital toxoplasmosis occurring in infants perinatally infected with human immunodeficiency virus 1. Pediatr Infect Dis J *9:* 512-518

Morgello S 1992 Epstein-Barr and human immunodeficiency viruses in acquired immunodeficiency syndrome-related primary central nervous system lymphoma. Am J Pathol *141:* 441-450

Pippard MJ, Dalgleish A, Gibson P, Malkovsky M, Webster ADB 1986 Acquired immunodeficiency with disseminated cryptococcosis. Arch Dis Child *61:* 289-302

Remington J, Desmonts G 1990 Toxoplasmosis. In: *Remington J, Klein J (eds)* Infectious diseases of the fetus and newborn infant. Saunders, Philadelphia, pp 89-195

Rubin LG, Gleit-Caduri D, Krilov LR 1989 Multiple opportunistic infections in an adolescent with AIDS, with recovery. Children's Hospital Quarterly *1:* 299-303

Scott GB, Fischl MA, Klimas N, Fletcher MA, Dickinson GM, Levine RS, Parks WP 1985 Mothers of infants with the acquired immunodeficiency syndrome. Evidence for both symptomatic and asymptomatic carriers. JAMA *253:* 363-366

Shanks GD, Redfield RR, Fischer GW 1987 Toxoplasma encephalitis in an infant with acquired immunodeficiency syndrome. Pediatr Infect Dis J *6:* 70-71

Singer C, Berger JR, Bowen BC, Bruce JH, Weiner WJ 1993 Akinetic-rigid syndrome in a 13-year-old girl with HIV-related progressive multifocal leukoencephalopathy. Mov Disord *8:* 113-116

The National Institute of Child Health, Human Development Intravenous Immunoglobulin Study Group 1991 Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. N Engl J Med *325:* 73-80

Ting SF, Glader BE, Prober CG 1991 Cryptococcus infection in a nine-year-old child with hemophilia and the acquired immunodeficiency syndrome. Pediatr Infect Dis J *10:* 76-77

Vandersteenhoven JJ, Dbaibo G, Boyko OB, Hulette CM, Anthony DC, Kenny JF, Wilfert CM 1992 Progressive multifocal leukoencephalopathy in pediatric Acquired Immunodeficiency Syndrome. Pediatr Infect Dis J *11:* 232-237

Vinters HV, Kwok MK, Ho HW, Anders KH, Tomiyasu U, Wolfson WL, Robert F 1989 Cytomegalovirus in the nervous system of patients with the acquired immune deficiency syndrome. Brain *112:* 245-268

Wahn V, Kramer HH, Voit T, Bruster HT, Scrampical B, Scheid A 1986 Horizontal transmission of HIV infection between two siblings. Lancet *694:*

Walsh TJ, Butler KM 1991 Fungal infections complicating pediatric AIDS. In: *Pizzo PA, Wilfert CM (eds)* Pediatric AIDS. The challenge of HIV infection in infants, children, and adolescents. Williams and Wilkins, Baltimore, pp 225-244