Pathogens in children with severe combined immune deficiency disease or AIDS

Dominique Lauzon, MD
Gilles Delage, MD
Pierre Brochu, MD
Jean Michaud, MD
Gaétan Jasmin, MD
Jean H. Joncas, MD
Normand Lapointe, MD

We evaluated the frequency and severity of illnesses caused by various microbial pathogens in 15 children with severe combined immune deficiency disease (SCID) and 8 with acquired immune deficiency syndrome (AIDS). There were 35 viral, 23 bacterial, 19 mycotic and 13 parasitic infections. Nineteen of the 23 patients died of infection; *Pneumocystis carinii* pneumonia, giant-cell pneumonia due to paramyxoviruses and various disseminated viral infections were responsible for most deaths in both groups. The emerging role of paramyxoviruses was illustrated by the fact that they were responsible for giant-cell pneumonia in seven patients. Viral enteric infections were frequent in both groups. The variety of infectious microorganisms and the severity of resulting illnesses in the patients with AIDS were similar to those in the patients with SCID.

Nous avons étudié la fréquence et la sévérité des infections causées par divers microorganismes chez 15 enfants atteints du déficit immunitaire mixte et grave et chez 8 enfants atteints du syndrome d'immunodéficience acquise (SIDA). Trente-cinq infections virales, 23 infections bactériennes et 19 infections fongiques sont dénombrées, ainsi que 13 infestations parasitaires. Dix-neuf malades sur 23 sont décédés d'infection: la plupart des décès dans les deux groupes ont été causés par une pneumonie à *Pneumocystis carinii*, une pneumonie à cellules géantes à paramyxovirus ou une infection virale disséminée. L'importance des paramyxovirus est mise en relief par le fait qu'ils ont déterminé une pneumonie à cellules géantes chez sept malades. Les infections gastrointestinales virales sont nombreuses dans les deux groupes. L'éventail des agents microbiens et la gravité des infections sont comparables dans les deux groupes de malades.

From the departments of Microbiology and Immunology, Pathology and Pediatrics, hôpital Sainte-Justine, Montreal, and université de Montréal

Reprint requests to: Dr. Gilles Delage, Department of Microbiology and Immunology, hôpital Sainte-Justine, 3175 Côte St. Catherine Rd., Montreal, PQ H3T 1C5

Severe, often fatal, infections due to a variety of microorganisms develop in patients with severe combined immune deficiency disease (SCID).[1] The prevalence of various infectious agents has been studied in several groups of such patients.[2-4]

A new syndrome of acquired immune deficiency disease associated with opportunistic infections has been recognized since 1981.[5] Recently, cases have been described in children.[6-9]

In this paper we present data concerning the role of various infectious agents in the sickness and death of 23 children with severe immune deficiency diseases, 8 of whom had acquired immune deficiency syndrome (AIDS).

Patients

Fifteen patients with SCID and 8 with AIDS were seen between 1966 and 1985, 20 of them since 1975. Basic data on the patients, including the microorganisms found, are summarized in Tables I and II. Autopsies were performed on the 19 patients who died.

Of the 15 patients with SCID 3 had X-linked disease. Adenosine deaminase deficiency was proved directly or through family history in five

patients. The mode of transmission could not be defined in seven patients with typical SCID; only one of them (patient 6) belonged to a group at high risk for AIDS. This patient was a Haitian girl who died in 1976 at 6 months of age of a severe cellular and humoral deficit characterized by agammaglobulinemia and severe lymphopenia complicated by *Pneumocystis carinii* pneumonia. Her mother has recently been seen and is in good health; she has no anomalies of cellular or humoral immunity and has no antibodies to human T-lymphotropic virus type III (HTLV-III). Patients 4 and 7 as well as all those studied since 1980 had an absence of or constant decrease in the number of mature T cells, a profound alteration of T-cell function and hypogammaglobulinemia. The others (patients 1, 2, 3, 5 and 6) all had hypogammaglobulinemia and various degrees of lymphopenia. All autopsies revealed classic thymic dysplasia and generalized depletion of lymphocytes in lymphoid organs. Patients 7 through 9 and 12 through 15 had no antibodies to HTLV-III.

The diagnosis of AIDS in our first patient (patient 16), a Haitian girl, was based on the development of *P. carinii* pneumonia and disseminated cytomegalovirus (CMV) infection. Her mother died of an undifferentiated lymphoma with acute miliary tuberculosis 6 weeks after giving birth. Autopsy of the child revealed widespread depletion of lymphocytes in lymphoid organs; hypogammaglobulinemia was documented before death. All other patients with AIDS had a depressed count of helper T cells in peripheral blood and an inverted ratio of helper to suppressor T

Table I — Demographic and pathological features of 15 children with severe combined immune deficiency disease (SCID)

Patient no./sex	Year of diagnosis	Outcome (and age, mo)	Pathogens (form of disease)
1/M*	1966	Died (8)	Measles virus, *Streptococcus pneumoniae, Staphylococcus aureus, Candida albicans, Pneumocystis carinii*†
2/M	1966	Died (6)	*S. pneumoniae,* gram-negative rod,† *C. albicans*
3/M‡	1969	Died (3.5)	*Pseudomonas aeruginosa*
4/M	1975	Died (9)	Parainfluenza type 3 virus, *Klebsiella pneumoniae,*† *Mycobacterium tuberculosis,*† *C. albicans* (mucocutaneous + esophageal), *P. carinii*†
5/M‡	1976	Died (10)	Herpesvirus,† *Escherichia coli, C. albicans* (mucocutaneous + esophageal)
6/F	1976	Died (6.5)	*P. carinii*†
7/M*	1977	Died (5)	Parainfluenza type 3 virus,† *S. aureus, Salmonella typhimurium,*† *C. albicans*
8/F‡	1980	Died (10)	Rotavirus, echovirus 30, *S. aureus, E. coli, C. albicans, Candida parapsilosis, P. carinii*
9/F‡	1981	Died (32)	Parainfluenza type 3 virus, cytomegalovirus (CMV), rotavirus, noncultivable picorna- or parvo-like virus (NCPP), poliovirus 2, Epstein–Barr virus,† *P. carinii*
10/M	1981	Died (8)	Parainfluenza type 3 virus, respiratory syncytial virus (RSV), adenovirus type 4, nontypable adenovirus,† *S. aureus, E. coli, Acinetobacter* sp., group A *Streptococcus, Staphylococcus epidermidis, C. albicans, Aspergillus fumigatus*
11/M*	1982	Died (6)	RSV,† *S. aureus, C. albicans, P. carinii*†
12/M	1982	Died (35)	Adenovirus, enterovirus, influenza A virus, *C. albicans, A. fumigatus,*† *Giardia lamblia*
13/F‡	1984	Died (8)	RSV,† adenovirus, rotavirus, NCPP
14/M	1984	Alive (16)	*P. carinii*
15/F	1984	Alive (9)	*S. pneumoniae, C. albicans*

*Patient had X-linked SCID.
†Microorganism responsible for death.
‡Patient had adenosine deaminase deficiency.

Table II — Demographic and pathological features of eight children with acquired immune deficiency syndrome (AIDS)

Patient no./sex	Year of diagnosis	Outcome (and age, mo)	Pathogens
16/F	1981	Died (6)	CMV,* *S. pneumoniae,* C. albicans, P. carinii*
17/F	1982	Died (13)	CMV, *P. carinii**
18/M	1982	Died (44)	NCPP, *E. coli, C. albicans*
19/F	1983	Died (8)	Parainfluenza type 3 virus, adenovirus, echovirus 22, *S. pneumoniae, C. albicans, P. carinii**
20/F	1983	Alive (23)	CMV, echovirus 22, poliovirus 2, *Streptococcus salivarius, C. albicans*
21/M	1984	Died (7)	CMV,* *C. albicans*
22/M	1985	Died (7)	*C. albicans, P. carinii*
23/F	1985	Alive (24)	Herpes simplex virus, *Cryptosporidium* sp.

*Microorganism responsible for death.

cells; all had antibodies to HTLV-III. Five patients had hypergammaglobulinemia, whereas two had decreased immunoglobulin levels. In addition, all but one of the seven either suffered from or died of a severe opportunistic infection. Lymphocytic interstitial pneumonia, confirmed by lung biopsy, developed in one patient who later died of complications of chronic progressive encephalopathy. The general characteristics of the first six patients with AIDS have been reported elsewhere.[10]

Patients with an immune deficiency secondary to immunosuppressive therapy, chemotherapy or radiotherapy were excluded.

All biopsy and autopsy slides were reviewed by two of us. Data on all infections documented by histologic or microbiologic means, or both, were compiled. Infections were considered the cause of death if clinical signs and symptoms or autopsy findings of overwhelming infection were present.

Results

There were 35 viral, 23 bacterial, 19 mycotic and 13 parasitic infections in our patients. The microorganisms that caused infections are listed in Table III.

Fatal infections were due to *P. carinii* in eight patients, viruses in eight, bacteria in five and *Aspergillus fumigatus* in one. In four patients, death was caused by more than one microorganism. Three patients died of causes other than documented infection. Patient 3 died of severe pneumonia; histologic examination of the lung at autopsy did not reveal any microorganisms, and the tissue was not cultured. Patient 8 died of a progressive neurologic disorder related to an enzyme deficiency. Patient 18 died as a result of chronic progressive encephalopathy; detailed results of the neuropathological examination of this patient will be reported elsewhere.

Table III—Microorganisms that caused infections in the patients

Microorganism	No. of patients
Viruses	
Parainfluenza type 3 virus	5
RSV	3
Adenovirus	5
CMV	5
Rotavirus	3
NCPP	3
Enterovirus	6
Other	5
Bacteria	
S. pneumoniae	5
S. aureus	5
Gram-negative rod	9
M. tuberculosis	1
Other	3
Fungi	
C. albicans	16
C. parapsilosis	1
A. fumigatus	2
Parasites	
P. carinii	11
G. lamblia	1
Cryptosporidium sp.	1

The respiratory tract was the major site of infection in our patients. Thirty-five microorganisms were isolated or documented histopathologically in 20 patients. *P. carinii* pneumonia was documented at biopsy or autopsy in 11 patients, 8 of whom died. Five patients did not respond to treatment with co-trimoxazole and pentamidine. In two other cases, treatment had been successful, but the disease recurred after therapy was stopped; treatment was not resumed and both patients died. Patient 1 was not treated for his infection.

Of the 13 viruses responsible for respiratory tract infections, 10 were paramyxoviruses or influenza virus, 2 were CMV and 1 was an adenovirus. Giant-cell pneumonia due to a paramyxovirus developed in seven patients, three of whom died; the causative viruses were parainfluenza type 3 virus in four patients, respiratory syncytial virus in two and measles virus in one.

Cases of interstitial pneumonia due to influenza A virus (in patient 13) and CMV (in patients 9 and 20) were also documented by lung biopsy. Bacterial lung infection was documented in only two patients, both of whom died; one infection was due to *Klebsiella pneumoniae* and the other to an unidentified gram-negative rod. Two patients had an infection of the lung caused by *Aspergillus* that was documented histologically; one died because of extensive involvement.

The digestive tract was frequently involved. Oropharyngeal candidiasis, associated with skin involvement in four cases, was found in 16 of 23 patients; 2 patients had esophageal candidiasis. None of these infections became disseminated. Eighteen viruses were found in the gastrointestinal tract in 10 cases: adenovirus (in 4 cases), picorna- or parvo-like virus that could not be cultivated (in 3), rotavirus (in 3), echovirus 22 (in 2), CMV (in 2), poliovirus type 2 (in 2), echovirus 30 (in 1) and herpesvirus (in 1). Numerous viral particles were present in the cytoplasm of duodenal epithelial cells in patient 12 (Fig. 1), who for many weeks had excreted a picorna- or parvo-like virus that could not be cultivated; this patient had previously had a severe malabsorption syndrome due to an infestation with *Giardia lamblia* and had responded to metronidazole therapy. In the cases of CMV and echovirus 30 infection, gastrointestinal involvement was part of disseminated infection; the two patients with CMV infection died of extensive involvement of the gastrointestinal tract, lung, liver, kidney and central nervous system.

Patient 5 died of necrotizing hepatitis; electron microscopic examination of liver tissue obtained at autopsy revealed herpesvirus particles. The tissue was not cultured. Patient 10 died of necrotizing pancreatitis and hepatitis due to an adenovirus that could not be typed with antisera to types 1 to 7.

All patients with a viral infection of the gastrointestinal tract had prolonged excretion of the virus. The two patients with excretion of poliovirus type 2 were asymptomatic. One patient died of gastroenteritis and septicemia due to *Salmonella typhimurium*, which did not respond to 20 days of antibiotic therapy. One of the patients with AIDS had severe protracted diarrhea due to *Cryptosporidium* sp.

Eleven cases of severe bacterial infection were documented, five of which were associated with the patient's death; these included one case of disseminated tuberculosis and one of pericardial effusion due to *Streptococcus pneumoniae*. Five cases of bacteremia (two due to *S. pneumoniae* and one each due to *Staphylococcus aureus, Staphylococcus epidermidis* and *Streptococcus salivarius*) and one case of pneumococcal meningitis responded well to antibiotic therapy.

Skin infection due to *Staphylococcus aureus* was found in four patients but was superficial and well controlled with antibiotic therapy. Recurrent herpetic whitlow and stomatitis in a patient with AIDS were successfully treated with acyclovir. Urinary tract infection due to *Escherichia coli* occurred in four patients. Two cases of otitis media due to *Pseudomonas aeruginosa* and *Acinetobacter* sp., one case of pharyngitis due to group A streptococci and one case of conjunctivitis due to *S. pneumoniae* were also found.

In patient 10 a fatal multifocal lymphoproliferative disease developed that involved the brain, lungs, liver, lymph nodes, spleen, kidney and adrenal glands. Results of immunofluorescence studies showed that the disease was caused by Epstein-Barr virus (EBV).[11]

The microorganisms detected in the patients with AIDS were similar to those found in the patients with SCID. *P. carinii* pneumonia and viral infection of the gastrointestinal tract as well as oropharyngeal candidiasis were frequent in both groups. However, viral infections of the respiratory tract were more frequent in the SCID group; the one case in the AIDS group was giant-cell pneumonia due to parainfluenza type 3 virus.

Discussion

Infections were the major cause of sickness and death in our patients, causing 17 of the 19 deaths. *P. carinii* was the single most common microorganism that caused fatal infection in our patients. The high prevalence of infections due to *P. carinii* in severe immune deficiency diseases was confirmed in our study: 11 (48%) of our 23 patients had pneumonia due to this organism. Leggiadro and colleagues,[2] in a survey of 33 centres providing care for patients with SCID, found an overall prevalence rate of *P. carinii* pneumonia of 27%; the rate in patients who had not received antimicrobial prophylaxis was 42%.

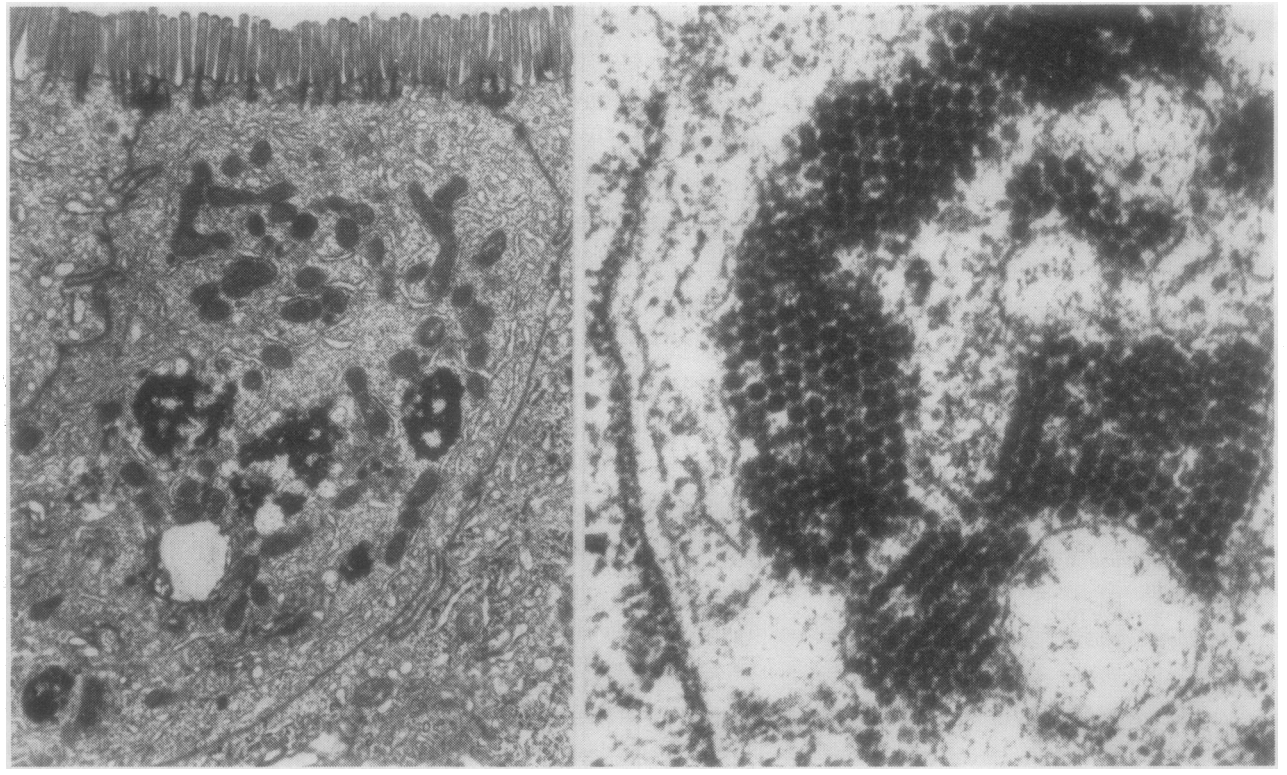

Fig. 1 — Left: low-power electron micrograph of epithelial cell from jejunal mucosa, showing intracytoplasmic aggregates of dense particles (Epon section, uranyl acetate-lead citrate; ×9900, enlarged approximately 3%). Right: higher magnification of dense aggregates, showing crystalline arrays of picorna- or parvo-like virus particles. Note polyhedral aspect of virions, whose core measures 18.5 nm in diameter (×154 400, enlarged approximately 4%).

In a study of 69 children with SCID who were undergoing immunologic reconstitution, 13 were found to have *P. carinii* infection before bone marrow transplantation.[12] *P. carinii* pneumonia also frequently occurs in children with AIDS.[6,7,9]

The finding that a high proportion of our patients had viral infections of the respiratory tract agrees with the recent report of Jarvis and associates,[4] who showed that viruses were the main cause of sickness and death in patients with SCID. In their study, paramyxoviruses caused 7 of 13 respiratory tract infections and were responsible for 5 deaths. In our study, paramyxoviruses caused seven cases of giant-cell pneumonia, three of which were partly or totally responsible for the patient's death. We also had one patient with pneumonia due to influenza A virus. Until recently, only measles virus was known to cause giant-cell pneumonia in patients with SCID.[13] Since 1974 seven cases of giant-cell pneumonia due to paramyxoviruses have been reported.[14-18] Fishaut and coworkers[19] described persistent infection due to respiratory viruses in patients with cellular immune defects. Thus, paramyxoviruses have only recently emerged as major pathogens in patients with SCID.

Persistent involvement of the gastrointestinal tract by enteric and other viruses has recently been documented in patients with SCID.[4,20] This phenomenon was noted in our more recent patients, who were systematically studied for viral infection of the gastrointestinal tract. As Jarvis and colleagues[4] noted, the ready demonstration of large quantities of viral particles by electron microscopy suggests that a major involvement of the infection site must be occurring. This was confirmed in one of our cases, in which a duodenal biopsy specimen showed epithelial cells containing many viral particles.

We documented five cases of fatal disseminated viral infection. One patient died of adenovirus hepatitis and pancreatitis. A few cases of fatal adenovirus infection have been reported in SCID;[4,21] severe hepatic involvement is usually found, as in our case. Two patients with AIDS were found to have severe disseminated CMV infection at autopsy. Such infection has occasionally been a cause of death in patients with SCID.[4,22] CMV is also known to cause severe infections in adults with AIDS;[5] recently, cases of lung involvement in children with AIDS have been reported.[6,8] Both our patients contracted the infection before 6 months of age. However, the insidious onset in both cases, with subsequent development of severe disease, confirmed at autopsy, strongly suggests that this was not a congenital infection but, rather, an acquired severe opportunistic infection. As a rule, severe disease in congenital CMV infection is clinically evident at birth.[23] One patient with adenosine deaminase deficiency died of disseminated B-cell lymphoproliferation associated with EBV; lymphomas of this nature have recently been recognized in patients with SCID.[24] This type of lymphoma has also been found with increasing frequency in patients who have undergone kidney or heart transplantation.[25,26] Immune deficiency therefore plays a major role in the development of such tumours.

One patient died of necrotizing hepatitis; herpesvirus-like particles were shown by electron microscopy. Unfortunately, herpes simplex virus (HSV) antigen could not be detected by means of immunoperoxidase studies of formaldehyde-fixed tissue, and no autopsy specimen of the liver was sent for viral culture. However, the histologic appearance and the presence of herpesvirus-like particles strongly suggested that either HSV or CMV was the causative agent. Fatal HSV infections appear to be rare in SCID; none were reported in three studies of 105 patients.[4,12,27] Necrotizing hepatitis due to HSV has been described in adults with various underlying conditions,[28] in pregnant women[29] and in malnourished children,[30] and is a characteristic finding in neonatal infection.[31] A case of disseminated HSV infection with necrosis of the liver in a young adult with unsuspected thymic dysplasia has been reported.[32] Necrotizing hepatitis due to CMV has been described in patients who have undergone renal transplantation.[33]

Persistent mucocutaneous *Candida albicans* infection was frequent and was often the first infection that led us to suspect an immune deficiency disease; no infection, however, became disseminated. Apparently, this yeast rarely causes invasive infections in SCID, except after bone marrow transplantation.[3] Two cases of *C. albicans* meningitis in patients with SCID have recently been described.[34] Invasive aspergillosis occurred twice in our patients but has not previously been reported in patients with SCID or AIDS. The emergence of this pathogen in SCID could be related to the longer survival of patients and the extensive use of life-support systems late in the disease.

The infectious agents found in our patients with AIDS were similar to those reported to date in children with the disease. Persistent oropharyngeal candidiasis, *P. carinii* pneumonia and chronic CMV infections have been reported to be predominant, along with invasive *Salmonella* infection and sepsis due to *S. pneumoniae*.[6,9,35] One finding of interest was the absence of *Mycobacterium avium–intracellulare* infection in our patients with AIDS. Disseminated infection due to this organism is quite frequent in adults with AIDS; in one series 9 of 25 patients were affected.[36] In a recent surveillance report of the US Centers for Disease Control, however, only 3 of 35 children with AIDS had disseminated *M. avium–intracellulare* infection.[37] The absence of toxoplasmosis in our patients with AIDS may be related to the fact that most cases were diagnosed when the patient was too young to have had exposure to the parasite.

The variety of infectious microorganisms and the severity of resulting illnesses in our patients with AIDS were comparable to those found in our

patients with SCID. Thus, both patients with SCID and those with AIDS appear to be highly susceptible to severe, persistent infections due to a variety of microorganisms, of which viruses appear to be the most common. The recent development of antiviral agents, particularly ribavirin, effective against many of these pathogens has led to new methods for treating opportunistic viral infections in these patients. Preliminary data are encouraging.[38,39] Therefore, it is essential that facilities for rapid diagnosis of viral infection be developed in institutions providing care for such patients.

We thank Dr. Gerry Ahronheim for extensive review of the manuscript.

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