A SINGLE CENTRE RETROSPECTIVE 5 YEAR SURVEY OF INFECTIOUS COMPLICATION IN 85 CHILDREN WITH COMBINED IMMUNODEFICIENCY

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Abstract — Children with primary T-lymphocyte deficiency are more susceptible to infection by organisms such as bacteria, fungi, protozoa and virus. The isolation of an opportunistic organism or an unusually severe infection with higher grade pathogens, provide a clue to diagnosis of immunodeficiency. To determine the microorganisms causing recurrent or severe infections in children with T-lymphocyte deficiency, we carried out a retrospective case review of 85 patients with T-lymphocyte deficiency who were investigated at the Great Ormond Street Hospital for Children, NHS Trust, over the 5 year period between June 1, 1988 and June 1, 1993. The group of patients included 53 males and 32 females, among which 23 and 62 were diagnosed to present SCID and CID subtypes respectively. Among the 174 organisms isolated, these included bacteria (97 isolates), viruses (43 isolates), fungi (25 isolates) and parasites (9 isolates). The predominant sites of infections were mainly the gastrointestinal (60 out of 174) and respiratory tracts (49 out of 174). The most common bacterial infections, were with aerobic gram negative organisms (28 isolates), Pseudomonas aeruginosa (17 isolates), Enterococcus (12 isolates), C. difficile (10 isolates). Analysis of 43 viral infection showed that Rotavirus (10 isolates), Adenovirus (9 isolates), Herpes simplex (6 isolates), and Cytomegalovirus (6 isolates), were predominant pathogens. Candida albicans was the most commonly isolated fungi. Parasitic infections included P. carini and Cryptosporidium, 3 and 6 out of 9 cases. In our group of patients 16 patients died before bone marrow transplantation, due to infectious complication. Based on this study, we suggest that propylaxis against bacterial, viral, fungal and protozoa agents is a necessity to minimize infectious complications in T-lymphocyte deficient patients, awaiting a bone marrow transplantation.
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INTRODUCTION

Primary T-lymphocyte deficiencies are a diverse group of illnesses that occur as a result of genetic defects of T-lymphocyte differentiation and/or activation (1). They usually give rise to a combined immunodeficiency (CID) which is characterised clinically and immunologically by defects of B as well as T-lymphocytes (2,3). The more profound forms of this disorder have little or no residual T- or B-lymphocyte function and are collectively called severe combined immunodeficiency (SCID) (2,3).

The result of primary T-lymphocyte deficiency is an increased susceptibility to infection by organisms that are either pathogenic in the normal host or are opportunistic agents. Hence, the isolation of an apportunistic agent in a child or occurrence of an unusually severe infection, may provide a clue to the diagnosis of immunodeficiency. Although the susceptibility of these patients to bacterial, fungal, parasitic (4), and viral infections have been studied (5,6,7,8,9). When reviewing the literature, there are only few comprehensive paediatric surveys addressing the wide spectrum of infectious complications caused by bacterial, viral, fungal and parasites (10,11,12). The purpose of the present study was to determine the agents causing infectious complication in patients presenting with T-lymphocyte deficiency, who were admitted via tertiary referral Hospital, over the 5 year period during the 1988-1993.

PATIENTS AND METHODS

The criteria used for diagnosis of primary T-lymphocyte deficiency were (a) T-lymphopaenia, (b) an absence of lymphocyte proliferative responses to mitogens and antigens, (c) and the inability of B-lymphocytes to produce specific antibody (2,3,13). Children with a secondary T-lymphocyte deficiency, such as HIV infection or patients on immunosuppressive therapy were excluded. Patients who received a bone marrow transplant for primary T-lymphocyte deficiency were excluded from analysis for the period after transplantation. On the basis of these criteria, the result of 85 patients referred to Great Ormond Street Hospital for Children NHS trust, between June 1, 1988 and June 1, 1993 were reviewed in this study. Microbiological data which included results of cultures of blood, cerebrospinal fluid and bronchial lavage fluids were obtained on these patients. Bacteria were isolated using standard culture techniques, positive isolates were further identified using analytical profile index (API) system (Biomerieux Basingstoke Hants, UK). Clostridium difficile toxic effect was identified by inoculation of faeces on to human embryonic lung fibroblast (HEL) and neutralization with antitoxin. Candida was identified by API auxanogram,

Aspergillus by examination of the mycelial morphology and microscopy. For identification of Pneumocystis carinii, samples were stained and an indirect immunofluoresence test (Shield Diagnostic, Dundee, Scottland) was used. Cryptosporidium was detected with microscopy study (Modified Zhiel-Nelson stain). Following the virological techniques were used to identify the presence of viruses. The respiratory viruses were identified by indirect immunofluoresence methods using monoclonal antibodies (Centers for Disease Control, Atlanta, USA). Screening for Rotavirus, Astrovirus and Caliciviruses was performed by direct examination of negatively stained (potassium phosphotungstic acid) faecal samples in a Philips electron microscope. The presence of other vira agents was determined by inoculation of human embryonic fibroblasts and examination for the presence positive isolates were identified by neutralization with typing sera obtained from Central Public Health Laboratory London UK. Samples for Cytomegalo virus were examined using the DEAFF (detection of early antigen fluorescing foci) using E13 Monoclonal antibody (Clonatec supplied by TCS, Ltd, Slough, UK) and/or by isolation of virus in cell culture.

RESULTS

85 patients with T-lymphocyte deficiencies were identified over a five year period, these included 23 patients who fulfilled the criteria for a diagnosis of SCID and 62 patients had features of CID. The specific diagnoses in the two groups are shown in Table 1. Of 85 patients, 51 (60%) had one or more pathogens or opportunistic organisms, isolated during an infectious episode in CID 36/62 (57%) and in SCID 15/23 (65%). There was a significant difference between the median age of these two groups CID: 55 month (range, 2-155), SCID: 9 month (range, 2-63), $p<.01$). Of these 51 patients, 18 (35%), had 4 or more pathogenic agents isolated during subsequent infective episodes. Table 2 shows the number of microbiological isolates, sites of infections and the category of etiologic agents isolated in these patients. The overall mortality rate in this study was 28%. Sixteen patients (19%) died before bone marrow transplantation, due to infectious complication and 8 patients (9%) died after bone marrow transplantation (BMT), from BMT complication and infections.

Table 1. Diagnosis in 23 patients with severe combined immunodeficiency and 62 patients with combined immunodeficiency

SCID subtype	n	M/F	Median age (range) (in months)
AR SCID[1]	9	3/6	7 (1-23)
X-linked SCID	5	5/0	2 (1-9)
ADA deficiency[2]	4	1/3	3 (2-14)
Reticular dysgenesis	1	0/1	10
Ommen's syndrome	1	1/0	8
Undefined SCID	3	1/2	7 (5-63)
Total	23		
CID subtype			
ARCID	16	9/7	56 (12-136)
Wiskott-Aldrich syndrome	14	14/0	106 (40-172)
hyper IgM	9	9/0	57 (4-155)
MHC2 deficiency[3]	4	1/3	40 (10-128)
Skeletal dysplasia	1	0/1	6
DiGeorge syndrome	2	2/0	14 (2-27)
PNP deficiency[4]	2	2/0	51 (24-79)
Undefined CID	14	5/9	59 (5-120)
Total	62		

1. AR = proven autosomal recessive, 2. ADA = Adenosine deaminase 3. MHC = Major histocompatibility complex, 4. PNP = Purine nucleoside phosphorylase.

Table 2. Sites of infections and category of isolates in patients with T-lymphocyte deficiency (36 combined imunodeficiency / 15 severe combined immunodeficiency)

Sites	Total	Isolates (CID)	Isolates (SCID)
Bacteria	97	62 (24)	35 (10)
Blood	29	16 (7)	13 (5)
Respiratory	24	17 (8)	7 (4)
Gastrointestinal	24	18 (13)	6 (5)
Skin	5	4 (4)	1 (1)
Urine	15	7 (4)	8 (4)
Fungal	25	21 (14)	4 (4)
Blood	2	1 (1)	1 (1)
Respiratory	8	8 (7)	0
Gastrointestinal	12	11 (7)	1 (1)
Skin	2	0	2 (2)
Urine	1	1 (1)	0
Parasite	9	8 (8)	1 (1)
Respiratory	6	5 (5)	1 (1)
Gastrointestinal	3	3 (3)	0
Virus	43	26 (15)	17 (7)
Blood	2	1 (1)	1 (1)
Respiratory	11	8 (5)	3 (3)
Gastrointestinal	21	11 (8)	10 (6)
Skin	4	4 (3)	0
Urine	5	2 (2)	3 (3)
Total	174	117	57

Total referes to total No of isolates. Numbers in bracket refer to No of patients in each categgory.

Bacterial Isolates

Bacterial infections were predominant, with 97 isolates in 34 patients (62 isolates in 24 CID patients and 35 isolates in 10 SCID patients). Of 97 bacterial isolates, 29 were blood culture isolates from 12 patients (16 isolates in 7 CID, and 13 isolates in 5 SCID). Of 29 isolates from the blood, 15 were from peripheral samples, and 8 were from both peripheral and central or Hickman line catheters and 6 were from central or Hickman line. The most common blood isolates in our group of patients were Entrococcus (8 isolates) and Staph. epidermidis (6 isolates) (Table 3). The respiratory tract was also an important site of infection with bacterial pathogens, the most frequently isolated bacteria, being Pseudomonas aeruginosa. From gastrointestinal tracts 42% of isolates (10/24) were C. difficile species, 5/10 were associated with toxin production. Overall, the most frequently isolated bacteria, were Aerobic gram negative species with Pseudomonas aerugionsa being the most common. Acid-fast bacilli were cultured from wound exudate and respiratory secretion (BAL) from 1 patient (CID), these subsequently were identified as M. bovis. Another patient with CID had tuberculous colitis and colonic biopsies taken which grew M. fortuitum. The previously described patient had been vaccinated with BCG and developed disseminated BCG infection characterized by major skin and lung involvement. She died despite the treatment with INH and Rifampin and bone marrow transplantation at age 6 months.

Fungal and Parasite Isolates

Of 25 fungal isolates in 18 patients (21 in 14 CID patients and 4 in 4 SCID patients), Candida albicans was the most frequent isolate (Table 4) and was responsible mainly for oropharyngeal colonisation. Pneumocystis carinii was identified in bronchial alveolar lavage (BAL) specimens from 5 patients (4 CID, 1 SCID) and from lung biopsy material in 1 patient (CID). 3/6 patients died due to PCP despite ventilation and adequate therapy with high doses of cotrimoxazole. Cryptosporidium was isolated from gastrointestinal tract of 3 patients with CID (Table 4). All had severe diarrhoea. Only 1 patient (CID) responded to treatment (Spiramycin, Paromomycin); 1 patient died from associated complication.

Table 3. Distribution of bacterial species for positive bacterial cultures obained (36 combined immunodeficiency / 15 severe combined immunodeficiency)

Bacteria	Total	Blood	Respiratory	GI tract	Skin	Urine
Klebsiella sp	4	2/0	1/0	-	-	0/1
Enterobacter sp	8	2/2	-	-	-	1/3
Proteus sp	1	-	-	-	-	1/0
M. morgani	1	-	-	-	-	1/0
Serratia sp	1	-	-	1/0	-	-
Salmonella sp	3	-	-	3/0	-	-
E. coli	6	1/2	0/1	-	-	1/1
A. anitratus	1	-	1/0	-	-	-
C. freundii	2	-	-	1/0	-	0/1
Achromobacter	1	1/0	-	-	-	-
P. aeruginosa	17	-	5/4	3/2	1/1	1/0
Staph epi	9	5/1	1/1	0/1	-	-
Staph aureus	5	0/2	1/0	1/0	1/0	-
Strp. pneumonia	3	-	3/0	-	-	-
βHS Group B	1	0/1	-	-	-	-
αH Strep	3	1/0	2/0	-	-	-
Enterococcus	12	4/4	-	-	-	2/2
H. influenza	2	-	2/0	-	-	-
H. parainfluenza	1	-	0/1	-	-	-
C. difficile	10	-	-	8/2	-	-
C. perfringens	3	0/1	-	0/1	1/0	-
Myco. bovis	2	-	1/0	-	1/0	-
Myco. fortuitum	1	-	-	1/0	-	-
Total	97	16/13	17/7	18/6	4/1	7/8

Total refers to total No of isolates; M. Morgani: Morganella morgani; A. anitratus: Acinetobacter anitratus; C. freundii: Citrobacter freundii; P. aeruginosa: Pseudomonas aeruginosa; Step. pneumonia: Streptococcus pneumonia; βHS Group B: Beta haemolytic streptococcus Group B; αH Strep: Alpha haemolytic streptococcus; H. influenza: Haemophilus influenza; H. parainfluenza: Haemophilus parainfluenza; C. difficile: Clostridium difficile; Myco. bovis: Mycobacterium bovis; Myco. fortuitum: Mycobacterium fortuitum

Virus Isolates

There were 43 viruses identified in 22 patients (26 in 15 CID patients, and 17 in 7 SCID patients). Overall, Rotavirus, Adenovirus, CMV and Herpes simplex were the most common agents seen (Table 4). Of the 43 isolated viruses, 21 (49%) were detected in the GI tract, with the most frequently identified virus, being Rotavirus (5 isolates in 5 CID and 5 isolates in 5 SCID). In 6/10 patients excretion of virus was temporally associated with diarrhoea, and 2/10 of these patients (one with AR SCID and another with X-linked SCID) were shown to exrete Rotavirus from the gastrointestinal tract for 5 and 3 months respectively. Cytomegalovirus (CMV) was isolated in 4 patients (2 CID, 2 SCID). In these group of patients, one with CID, had CMV colitis and ileitis with intermittent episodes of intestinal obstruction which eventually lead to perforation and ileal resection. Respiratory syncytial virus (RSV) was detected in 2 patients (1 SCID, 1 CID), the patinet with SCID, had prolonged shedding of RSV from the respiratory tract which lasted for the period of the final 14 months of her life. This patients was also shown to excreting Rotavirus and Calicivirus in the gastrointestinal tract for period of 5 months following the first bone marrow transplantation. Adenovirus was isolated in 5 patients (3 CID, 2 SCID), in this group, one patient with SCID (ADA deficiency), had disseminated Adenovirus infection, manifested by lung disease, severe hepatitis and myocarditis. Adenovirus was isolated from Buffy coat, respiratory and gastrointestinal tracts. He did not respond to antiviral therapy with intravrnous and nebulized ribavirin and died at age of 14 months. Among the 10 patients (3 SCID, 7 CID) who received oral poliovirus vaccine, virus was detected in stool of 1 CID and in nasopharyngeal secretions of another patient with CID, but none subsequently developed disseminated disease.

DISCUSSION

In our study we were able to identify and isolated organisms in 60% of patients (36/62 CID, 15/23 SCID). The median age of patients with SCID who had a documented isolate was significantly less than in those diagnosed with CID. This would be in keeping with the fact that patients with SCID develop infection earlier than patients with CID (2). Although infections in patients with SCID are often more frequent and more severe, the absence of documented infections in 8/23 of our patients with SCID, reflects their early diagnosis. In this group of 8 patients, 2 received a bone marrow transplant at the age of 1 month, 3 between the age of 1-7 months, and 1 at the age of 11 month. The medical records of 1 patients with SCID could not be located.

Children with primary T-lymhocyte deficiency are more susceptible to infections by both organisms that are pathogenic in the normal host and opportunistic organisms which include bacteria, virus, protozoa and fungi (13). Clinical presentation is often with failure to thrive and increased severity and frequency of infections, which tend to occur earlier in children with SCID than

Table 4. Distribution of fungal / parasite / viral species for positive cultures (36 combined immunodeficiency / 15 severe combined immunodeficiency)

Fungal / Parasite	Total	Blood	Respiratory	GI tract	Skin	Urine
Fungal						
Candida albicans	24	1/1	7/0	11/1	0/2	1/0
Aspergillus flavus	1	-	1/0	-	-	-
Total	25	1/1	8/0	11/1	0/2	1/0
Parasite						
P.carinii	6	-	6/1	-	-	-
Cryptosporidium	3	-	-	3/0	-	-
Total	9	-	5/1	3/0	-	-
Viruses						
Herpes virus	6	-	1/0	1/0	4/0	-
CMV	6	1/0	1/0	-	-	2/2
RSV	2	-	1/1	-	-	-
Para.influenza Type 3	1	-	1/0	-	-	-
Adenovirus	9	0/1	2/2	1/2	-	0/1
Rotavirus	10	-	-	5/5	-	-
Astrovirus	2	-	-	1/1	-	-
Calicivirus	1	-	-	0/1	-	-
SRSv	2	-	-	1/1	-	-
Enterovirus	2	-	1/0	1/0	-	-
Poliovirus	2	-	1/0	1/0	-	-
Total	43	1/1	8/3	11/10	4/0	2/3

Total refers to total No of isolates; P. carinii: Pneumocystis carinni; CMV: Cytomegalo virus; RSV: Respiratory syncytial virus; SRSV: Small rounded structured virus.

in the those with CID (14,15). In patients with CID and SCID, because of inability of their B - lymphocytes to produce specific antibodies, diagnosis of viral infection by antibody determination are little or no value (13). Direct viral isolation and/or identification of the viral genome (PCR) are necessary to prove infection. Virus isolation in cell cultures in the reference method, but results are often delayed.

Of the 97 bacterial pathogens isolated from our group of patients, the majority were cultured from the blood (14), respiratory tract (9) and gastrointestinal tract (10). A retrospective study of 117 infants and children with SCID at the Necker's Hospital in Paris (12), showed that infections were the major cause of death, with lung and gastrointestinal tract as the prodominant sites involved, and the most common bacterial isolates were Pseudomonas spp, Escherichia coli, and Streptococci. In their study disseminated BCG infection (BCG-osis), occurred in more than one third (10/28) of patients who had previosuly received BCG vaccine. The infection was fatal in three cases. In our group of patients, 3 infants (1 SCID, 2 CID) received BCG vaccination at birth. One patient (CID) developed disseminated BCG infection. Disseminated BCG infection in the severely immunocompromised host has high mortality. Gonzales et al (16), reported fatal BCG infection in 9 patients with an immunodeficiency syndrome (2 SCID, 4 CID, 3 CGD). Four patients with CID presented with regional lymphadenitis resistant to treatment after five month of life, all four patients died despite prolonged specific treatment. Bone marrow transplantation with appropriate anti-mycobacterial therapy, may lead to successful resolution of disseminated BCG osis (17). Immunomudolatory therapy with IFN-γ which has been used in treatment of refractory dissiminated nontuberculous mycobacterial infection (18), may also have a place in the therapy of disseminated BCG infection in children with immunodeficiency.

Fungal and parasitic infections may be a major cause of mortality and morbidity in T-lymphocyte deficient children (19). In our survey, oral candidiasis was the most common fungal infection encountered. Surpirsingly few other major fungal infections were seen. A high incidence of candida infections in patients with T-lymphocyte dificiency have been reported by other groups (4,10,11). In contrast Muller et al (20), recorded only one case among 16 patients with DiGeorge syndrome. Among the parasitic infections seen in our group of patients, Pneumocystis carinii was the most common opportunistic infection. Pneumocystis carinii pneumonia (PCP), was diagnosed in 6 patients. Five of these patients developed symptoms under 6 months of age. We found a high mortality (50%) in our patients, who required ventilation. In children with AIDS and PCP, there is similar mortality in those who required ventilation (21). Walzer et al (4), reported that PCP was a major cause of infection in T-lymphocyte deficient patients associated with high mortality (13/20). The poor Prognosis may be explained by the fact that PCP is primary disease in young children rather than reactivation disease. In our survey Cryptosporidium, was isolated from the gastrointestinal tract of 3 patients with CID which resulted in severe and chronic diarrhoea. Acute C.parvum infection in immunocompetent persons, usually induces a short and self-limited diarrhoea with a specific immune response that eliminates the protozoan after 1-8 weeks (22). C. parvum infection in T-lymphocyte deficient children (11), especially in AIDS patients, may cause chronic and life-threatening diarrhoea.

Viral infections of the lungs, liver and central nervous system are usually severe and extensive in the immunocompromised patients (7). In a retrospective study of 30 patients with MHC class 2 (CID) dificiency carried out by Klein and colleagues (11), the main cause of death was viral infection. In our study, of the 43 virus isolated, the majority were from gastrointestinal tract (Rotavirus), respiratory tract (Adenovirus) and skin (Herpes virus). In the group of patients with CID one had complicated CMV colitis and ileitis. Ulceration associated with CMV infection could be identified in the oesophagus, the stomach, the small bowel, and large intestine (23). One controlled study using ganciclovir showed that despite an antiviral effect, there was no significant improvement in the clinical course (24). However, on the basis of clinical experience in therapy CMV interstitial pneumonia, it is common practice to use the ganciclovir/intravenous immunoglobulin combination according to the treatment regimen for CMV interstitial pneumonia (25). Herpes simplex often caused mild infection in our group of patients with involvement of mucocutaneous areas in 4 patients with CID. These rapidly responded to treatment with acyclovir. Varicella infections were not seen in our group patients. In one of our patient with SCID, despite repeated treatment courses with nebulized ribavirin, RSV was shed from her respiratory tract for the last 14 months of her life during which she received two unsuccessful haploidentical bone marrow transplantation. Respiratory syncytial virus may cause prolonged viral shedding in immunodeficient children. The virus is difficult to eradicate unless the T-cell eficiency is corrected (19). In one of our patients (1 SCID). dissemination with Adenovirus occurred. This was manifested by lung disease and severe hepatitis which lead to hepatic failure. In T-lymphocyte deficient patients, initial infection with adenovrius usually occurs in respiratory tract, but in the absence of adequate T-lymphocyte response, dissemination may occur (19). Live polio vaccination did not lead to disseminated diesease, possibly because patients had been vaccinated

at an early age, when maternal IgG was present and protective (12). We carried out a retrospective study on infectious complications in 85 children with T-lymphocyte deficiency treated in this Hospital over a 5 years period between June 1, 1988 and June 1, 1993. The group of patients included 53 males and 32 females, among which 23 and 62 were diagnosed to present SCID and CID subtypes respectively. Among the 174 organisms isolated, these included bacteria (97 isolates), viruses (43 isolates), fungi (25 isolates) and parasites (9 isolates). The predominant sites of infections were mainly the gastrointestinal (60 out of 174) and respiratory tracts (49 out of 174). The most common bacterial infections, were with aerobic gram negative organisms (28 isolates), Pseudomonas aeruginosa (17 isolates), Enterococcus (12 isolates), C. difficile (10 isolates). Analysis of 43 viral infection whowed that Rotavirus (10 isolates), Adenovirus (9 isolates), Herpes simplex (6 isolates), and Cytomegalovirus (6 isolates), were predominant pathogens. Candida albicans was the most commonly isolated fungi. Parasitic infections included P. carinii and Cryptosoridium, 3 and 6 out of 9 cases. In our group of patients 16 patients died before bone marrow transplantation, due to infectious complication. Based on this study, we suggest that prophylaxis against bacterial, viral, fungal and protozoa agents is a necessity to minimize infectious complications in T-lymphocyte deficient patients, awaiting a bone marrow transplantation.

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