Severe Combined Immunodeficiency-Classification, Microbiology Association, and Treatment

Subjects: Medicine, Research & Experimental

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Severe combined immunodeficiency (SCID) is produced by a defect in the functions and/or numbers of the immune cells (T and B cells). It manifests early in life. It can be fatal if it is left untreated. Numerous microorganisms including bacteria, viruses, fungi and parasites cause infectious diseases as pneumonia, meningitis, skin infections, gastrointestinal and many others. Stem cell transplantation at early age is the definitive treatment of choice and can cure the disease. Other treatment includes the use of antimicrobials, enzyme-replacement therapy and gene therapy.

Severe Combined immunodeficiency | Microorganisms | Stem cell transplantation | Antimicrobials

1. Viruses

Opportunistic Viral Infections eg. Cytomegalovirus, Epstein–Barr virus, Adenovirus, Enterovirus, Herpes Simplex Virus and Parainfluenza virus can cause severe disseminated infections in SCID patients, which can be fatal if left untreated or undiagnosed [1][2][3]. Cytomegalovirus (CMV) has been found to be excreted in breastmilk and breastfeeding should not be advised for SCID patients, unless the mother is found to be CMV antibody-negative [4].

Infection with Adenovirus can manifest as ocular, respiratory, gastrointestinal, or hepatic diseases in immunocompetent patients and is often mild and self-limiting [5]. However, in patients with SCID, adenovirus may produce severe and prolonged viral Pneumonia, Bronchiolitis, Hepatitis, or Gastroenteritis, with a potentially fatal outcome [6].

Rotavirus is the leading cause of severe gastroenteritis in children, and vaccination is the mainstay of prophylaxis [7]. However, the live rotavirus vaccine has been found to cause severe diarrhea in children with SCID, and should therefore be avoided [8]. Epstein–Barr virus infections affect over 95% of the human population at some point but are usually asymptomatic [9]. Symptomatic infections in adolescents may result in infectious mononucleosis characterized by fever, sore throat, splenomegaly, and lymphadenopathy. The virus typically attacks B cells; therefore, SCID patients with impaired or absent B cells are at an increased risk of EBV associated lymphomas as a result of persistent viremia and lymphoproliferation [10].

ParvoVirus-B19 is a common infection in rapidly dividing erythroid progenitor cells, with children being the main source of infection [11].Immunocompetent host infections can be asymptomatic or symptomatic, and include erythema infectiosum, arthropathy, anemia, thrombocytopenia, hepatitis, and myocarditis. In immunocompromised hosts, infection with Parvovirus B-19, chronic red cell aplasia, Acute Lymphoblastic Leukemia (ALL), and Virus-Associated Hemophagocytic Syndrome (VAHS) [12].

Varicella-zoster virus (VZV) infection occurs primarily via respiratory inoculation and establishes lifetime latency in the sensory ganglia of immunocompetent patients [13]. Immunocompromised patients are at an increased risk of complications, such as reactivation, Herpes zoster, retinal necrosis, and even death [13]. Worldwide vaccination via live VZV vaccines has prevented many of the complications of VZV infection [14], however, vaccination in SCID patients has been associated with disseminated infection [15] including vaccine-associated pneumonia [16] and should therefore be avoided.

2. Bacteria

Recurrent sinopulmonary infections are characteristic of primary immunodeficiencies such as SCID, and can result in severe complications. Lung abscess, empyema, and pneumatocele. The bacterial causes of pneumonia include Staphylococcus aureus, Pseudomonas spp., Mycobacterium bovis, and other atypical mycobacteria [17]. On clinical imaging, an important diagnostic clue in acute pulmonary infections in children with primary immunodeficiencies as they often lack a thymic shadow [18].

Clinical manifestations of SCID include gastrointestinal infections, chronic diarrhea, and failure to thrive. Gram-positive bacteria such as Staphylococcus aureus and gram-negative bacteria such as Klebsiella pneumoniae, Pseudomonas aeruginosa, Burkholderia, and Chryseobacterium [19]. SCID patients who lack immunoglobulins are at constant risk of recurrent infections with encapsulated bacteria [20].

Omenn syndrome is an autosomal recessive form of SCID that is usually T-B-NK+ and is highly fatal owing to recurrent opportunistic infections [21][22]. Skin sepsis is observed in patients with Omenn syndrome. Skin sepsis in Omenn syndrome can occur due to colonization by bacteria such as Staphylococcus Aureus, Streptococcus Pyogenes, Enterococcus, and gram-negative bacteria, such as Pseudomonas [21][23][24]. Cutaneous manifestations of bacterial infections include recurrent and life-threatening skin abscesses, folliculitis, impetigo, and furunculosis [25]. Survival rarely exceeds several months after birth in the absence of curative treatment.

3. Fungi

Invasive fungal infections (IFI) rarely occur in immunocompetent individuals and are more likely to occur in patients with primary immunodeficiencies. Opportunistic fungal infections seen in SCID are similar to those in patients with AIDS, and are usually caused by opportunistic fungi. Pneumocystis carinii, Histoplasma capsulatum, and Cryptococcus Neoformins [26]. Pneumocystis carinii pneumonia is the most common respiratory infection in SCID,

and is often co-infected with a respiratory virus [23]. Patients with SCID may be offered prophylactic treatment against Pneumocystis carinii to prevent fatal complications.

Patients with SCID are at increased risk of disseminated fungal infections, with invasive Candida albicans and Aspergillus being the most prominent microorganisms [27]. Other rare microorganisms implicated in SCID include Acremonium and Pichia [28][29]. Colonization of the skin, oropharynx, and gut by Candida albicans, typically manifests as persistent oral thrush, Pneumonia or Meningitis [28]. Hematopoietic stem cell transplantation is the definitive treatment for SCID, and fluconazole (3 mg/kg OD) is administered as prophylaxis against candidiasis and is generally tolerated [30].

Invasive aspergillosis (IA) is a life-threatening condition in immunocompromised children. Infection is typically acquired in the community or via nosocomial infections during hospital construction, renovation, and air-conditioning systems [31]. Bronchopneumonia is the most common presentation of infection with Aspergillosis in SCID, and other primary immunodeficiencies [32]. Other clinical manifestations of invasive aspergillosis include pleural effusion, pulmonary infarction, pulmonary thrombosis, and pleural effusion [33][34].

Cryptococcosis is a subacute or chronic systemic mycosis caused by Cryptococcus neoformans [35][36]. Cryptococcus neoformans is an opportunistic fungus that infects immunocompromised individuals. The respiratory tract is the primary portal of entry and has been found to be fatal because of overwhelming pneumonia in patients with SCID [35]. Cryptococcus neoformans was found in the skin lesions of a patient with SCID who presented with a maculopapular rash along with lobar consolidation. The treatment was refractory to medical management, but responsive to hematopoietic stem cell therapy [37].

4. Parasites

Parasitic infections are the dominant cause of gastrointestinal disease in patients with SCID. Protozoans eg. Giardia lamblia and Cryptosporidium spp. are the most common parasites affecting patients with SCID. Other implicated parasites included Schistosoma species, Blastocystis hominis, Fasciola species, and Trichostrongylus species [38]. The gastrointestinal tract is the largest lymphoid organ of the body [39]. GI manifestations are the second most common manifestations of PID after pulmonary disease [40]. Gastrointestinal disorders, such as chronic diarrhea, malabsorption, and abdominal pain, are seen in as many as 50% of patients with primary immunodeficiencies [41]. Giardia lamblia is a zoonotic protozoan parasite typically found in the small intestine of humans and various animals. Infections can be asymptomatic to mild diarrhea in immunocompetent patients or severe and chronic diarrhea and malabsorption in immunocompromised patients [42][43][44].

Cryptosporidium can cause severe and chronic enteropathy by releasing proinflammatory cytokines such as interleukin-8 (IL-8) in intestinal epithelial cells in patients with primary immunodeficiencies [45][46]. Disseminated cryptosporidiosis can lead to biliary tract disease, pancreatitis, pulmonary disease, and stunted growth in patients with SCID [45]. Disseminated cryptosporidiosis leading to overwhelming sepsis and death has been observed in patients with SCID [47]. Although the International Agency for Research on Cancer (IARC) has not considered

protozoans as carcinogens for humans [48], Cryptosporidium has been associated with colonic adenocarcinoma in SCID mice [49]; therefore, this possible complication should be made aware and infection in SCID patients treated promptly.

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