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Invasive fungal infections in congenital immunodeficiencies

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Abstract

Both acquired and congenital immunodeficiencies may be associated with increased susceptibility to invasive fungal infections (IFIs), depending on the type of immune deficit. IFIs frequently occur in patients with phagocytic and cellular immune defects, but are rarely observed in those with humoral or complement deficits. Among congenital immune disorders, chronic granulomatous disease and hyper-IgE syndrome are most frequently associated with IFIs; variable susceptibility to fungal pathogens is also seen in patients with severe combined immunodeficiency, X-linked hyper-IgM syndrome, Wiskott–Aldrich syndrome, DiGeorge syndrome, common variable immunodeficiency, defects in the interferon-γ–interleukin-12 axis, and myeloperoxidase deficiency. *Aspergillus*, *Candida*, *Cryptococcus*, *Histoplasma* and other fungal genera are variably implicated in causing invasive infections in these patients. Prompt diagnosis of IFIs in this patient population requires a high degree of suspicion, together with a knowledge of their clinical presentation and the limitations of diagnostic modalities. Apart from administration of appropriate antifungal agents, successful management often requires the addition of surgical intervention. Adjunctive immunotherapy may be considered, although this has not been systematically studied. Prophylactic interferon-γ and itraconazole administration have been shown to reduce the risk of IFIs in patients with chronic granulomatous disease; however, the possibility of infections with azole-resistant organisms following long-term itraconazole prophylaxis should not be overlooked.

Keywords: *Aspergillus*, *Candida*, chronic granulomatous disease, congenital immunodeficiencies, fungal infections, review

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Introduction

Although fungi are often implicated in superficial infections in humans, they rarely cause invasive disease in healthy individuals; the latter tends to occur in patients with impaired immune responses or in the presence of certain predisposing factors. Among immunocompromised patients at risk for invasive fungal infections (IFIs), those with congenital immunodeficiencies constitute a distinct group that has attracted scientific interest over the last decades, in view of important advances in immunology and mycology.

Congenital immunodeficiencies are hereditary disorders, mainly single-gene abnormalities, that result in impaired immune responses to a number of infectious stimuli. As a consequence, patients may present with recurrent, protracted or severe infections caused by common pathogens, or with infections caused by opportunistic organisms, including fungi [1]. Despite the well-described orchestrated interplay between innate and adaptive, humoral and cellular, immunity, congenital immunodeficiencies are still classified for practical purposes as those affecting mainly the humoral or cellular component, the phagocytic component, and the complement. A number of distinct, well-characterized immunodeficiency syndromes have also been described that do not clearly fall in one of the previous categories [1–3].

An effective host response against fungal pathogens requires the coordinated contribution of both innate and adaptive immunity. Neutrophils, mononuclear leukocytes and dendritic cells are involved in fungal cell recognition and damage. Both oxidative and non-oxidative mechanisms mediate intracellular killing or extracellular damage of fungal elements. Oxidative fungal damage is achieved through reactive oxygen intermediates generated by the enzymatic activity of NADPH oxidase and nitric oxide synthase [4].

Over the last two decades, the adaptive immune response against fungi has been thought to be regulated by the differentiation of $CD4^+$ T-cells towards T-helper type 1 (Th1) and

T-helper type 2 (Th2) cells. The Th1 response is mediated by the interleukin (IL)-12/interferon (IFN)-γ axis, and stimulates phagocytic activity, resulting in protection from fungal infections. The Th2 response involves the production of IL-4 and IL-10, which downregulate the action of Th1 cytokines [4,5]. Recently, a third subset of T-helper cells has been described, the T-helper type 17 (Th17) cells, which produce a distinct cytokine profile, including IL-17A (IL-17), IL-17F, IL-21 and IL-22. Th17 responses appear to be important for protection against mucosal *Candida* infections [6]. Recent studies, however, suggest that human host defences against *Aspergillus fumigatus* rely more on Th1 than on Th17 responses [7]. The role of humoral responses in host defence against fungal pathogens is less clearly defined than that of cellular immunity.

Consistent with the immune mechanisms involved in human host defences against fungi, IFIs rarely occur in patients with humoral or complement defects. Instead, they can be observed with increased frequency in those with phagocytic and cellular immune deficits (Table 1) [8]. In the present review, we will discuss IFIs in patients with congenital immune deficits, beginning with chronic granulomatous disease (CGD), which carries a higher risk of fungal infections than other immunodeficiencies.

CGD

This inherited disorder occurs with a prevalence of approximately 1/250 000 live births, and is characterized by the lack or significant reduction of superoxide-generating NADPH oxidase activity in phagocytic cells. In the absence of superoxide anion and other reactive oxygen species, the patient's neutrophils are unable to kill catalase-producing bacteria and fungi, including *Staphylococcus aureus* and *A. fumigatus*. They are also deficient in forming neutrophil extracellular traps, a distinct mechanism by which neutrophils entrap and kill microorganisms [9]. This ineffective phagocytic response in patients with CGD is associated with chronic inflammation and formation of granulomas [10,11]. The lack of reactive oxygen derivatives was recently shown to contribute to the hyperinflammatory phenotype through a dysfunctional kynurenine pathway of tryptophan catabolism [12]. Two-thirds of CGD patients have the X-linked recessive form, which results from defects in the *CYBB* gene encoding the gp91-*phox* subunit of the NADPH oxidase complex. The remaining one-third have the autosomal recessive form, which results from defects in the *CYBA*, *NCF-1* and *NCF-2* genes, encoding subunits p22-*phox*, p47-*phox* and p67-*phox*, respectively. Patients with autosomal recessive CGD have a milder course than those with the X-linked form [11]. Most IFIs among CGD patients are caused by *Aspergillus* species and, to a lesser extent, by *Candida* species and other fungal species [8].

TABLE 1. Congenital immune defects and risk of invasive fungal infection (IFI)

IFI unlikely	Variable risk for IFI
Humoral X-linked/autosomal recessive agammaglobulinaemia IgA deficiency[a]	Phagocytic Chronic granulomatous disease, Myeloperoxidase deficiency Leukocyte adhesion deficiency, Congenital neutropenias
Complement Classic, late or alternative complement defects Mannose-binding lectin pathway defects	Cellular and combined Severe combined immunodeficiency, DiGeorge syndrome X-linked hyper-IgM syndrome, Wiskott–Aldrich syndrome
	Other Hyper-IgE syndrome, defects in the IFN-γ–IL-12 axis

IL, interleukin; IFN, interferon.
[a]IFIs have been observed in patients with common variable immunodeficiency, possibly because of associated T-cell defects.

Invasive aspergillosis (IA) in CGD patients

Data regarding the prevalence, clinical presentation and management of IA among individuals suffering from CGD originate from small series, case reports and two large patient groups; the first comprises 368 patients from the US CGD registry, and the second 429 European patients [13,14]. When data from these two large cohorts are analysed, it appears that *Aspergillus* species are the most commonly isolated organisms from CGD patients with pneumonia (18–41% of cases), the most common organisms isolated from brain abscesses (38% of cases), and the first or second most common causes of osteomyelitis (22–35% of cases). *Aspergillus* species are rarely implicated in cases of liver abscess, lymphadenitis, arthritis and fungaemia among CGD patients. In these and other series, IA was the most common cause of death, accounting for at least one-third of fatalities [13–15].

Among the *Aspergillus* species causing invasive infection in CGD patients, *A. fumigatus* is the most common, followed by *Aspergillus nidulans* (teleomorph: *Emericella nidulans*). In a cohort of 23 cases of IA in CGD patients, 17 were caused by *A. fumigatus* and six by *A. nidulans* [16]. The relatively increased frequency of *A. nidulans* infections in this patient population contrasts with the fact that *A. nidulans* is an uncommon pathogen in individuals with other types of immunosuppression. Recently, infections caused by other *Emericella* species, including *Emericella quadrilineata*, *Emericella rugulosa* and *E. nidulans* var. *echinulata*, have been docu-

mented in a small number of CGD patients. In most of these cases, *Emericella* species had been previously identified incorrectly as *A. nidulans* by conventional methods [17]. Indeed, there are subtle morphological differences among *Emericella* species, which cannot be appreciated using light microscopy; molecular techniques are required for correct identification. Finally, IA caused by *Aspergillus flavus* has been recently reported in a CGD patient [18].

IA may be the presenting manifestation of CGD, usually occurring during the first two decades of life of affected individuals. The site most commonly affected is the lung. Up to one-third of patients may be asymptomatic, and IA can present as a pulmonary infiltrate in routine chest radiographs. If signs and symptoms of respiratory illness exist, these are not specific. The differential diagnosis in this case should include other causes of pulmonary infection commonly observed in CGD patients, including *S. aureus*, *Nocardia* species, *Burkholderia cepacia* and non-*Aspergillus* fungal pathogens; mixed infections may occur [13]. IA caused by *A. fumigatus* may also primarily affect other sites, including the bones, brain, liver and lymph nodes [18,19]. In contrast, primary extrapulmonary sites are rarely observed for *A. nidulans*; infections caused by this species usually originate from the lungs, and appear to be more aggressive than those caused by *A. fumigatus*. Dissemination or local extension to the adjacent pleura, chest wall and vertebrae frequently complicates *A. nidulans* pulmonary infections [16,19]. Indeed, most of the osteomyelitis cases caused by *A. nidulans* in CGD patients involve the ribs and vertebrae, as a result of contiguous spread of a primary lung lesion. This is not the case for *A. fumigatus* osteomyelitis, where at least half of the cases represent primary infections of the cranium, humerus, femur and tibia [20].

The histological picture of IA lesions in CGD patients contrasts with that in neutropenic hosts, which is characterized by angio-invasion, coagulative necrosis and paucity of neutrophils. By comparison, in CGD patients, discrete pyogranulomatous lesions are observed, with an abundance of neutrophils but intact hyphae, which are surrounded by histiocytes and lymphocytes. Occasionally, giant cell formation and foci of necrosis with microabscesses are found [19,21].

As for all opportunistic infections in immunocompromised hosts, a high degree of clinical suspicion is important for timely diagnosis of IA in CGD patients. High-resolution computed tomography is the imaging study of choice in cases of pulmonary infection. The so-called 'classic' radiological signs of IA (halo and air-crescent sign) are not usually observed; the findings are non-specific, including nodular lesions, perihilar infiltrates, and segmental or lobar consolidation. Magnetic resonance imaging has a role in the diagnosis of extrapulmonary lesions, including brain abscesses [22]. Among non-invasive diagnostic modalities, the serum galactomannan antigen assay appears to have reduced sensitivity in CGD hosts, possibly because of the lack of angio-invasion by fungal hyphae [21,23]. In addition, false-positive results have been frequently observed in young infants, and variable results have been reported regarding the specificity of the galactomannan assay in older children [24–27]. *Aspergillus* PCR and detection of (1,3)-β-D-glucan have not yet been standardized or adequately studied in CGD patients. Detection of fungal elements in bronchoalveolar lavage fluid and biopsy specimens may provide significant help in diagnosis [18,19].

The introduction of newer antifungal agents, including lipid formulations of amphotericin B, the newer triazoles and echinocandins, has broadened the therapeutic options for invasive aspergillosis. Species identification and *in vitro* susceptibility testing may help to optimize treatment choices. For example, *A. nidulans* appears to be less susceptible than *E. quadrilineata* to amphotericin B and more susceptible to caspofungin [17]. Azole resistance may be observed after long-term azole prophylaxis in CGD patients (see below) [28,29].

Besides antifungal agents, adjunctive therapy with interferon (IFN)-γ has been used in a number of cases [30,31]. Limited clinical data also suggest a role for granulocyte transfusions from healthy donors in order to partially restore the patients' impaired phagocytic activity [32–34]. Finally, appropriate surgical debridement should not be delayed when needed, particularly in cases of localized (liver abscess and osteomyelitis) or aggressive lung infection [16].

The increased risk of infectious complications in CGD patients has led to the introduction of prophylactic strategies over the last two decades. Prophylactic subcutaneous administration of IFN-γ, three times a week, was associated with a reduction in the frequency of serious infections [35,36]. Daily administration of itraconazole was well tolerated, and significantly reduced the frequency of severe IFIs among CGD patients [37]. However, the possibility of breakthrough infections with azole-resistant *Aspergillus* strains following long-term itraconazole prophylaxis should not be overlooked [28,29]. Haematopoietic stem cell transplantation is currently the only proven curative treatment for CGD in selected patients; gene replacement therapy has been used experimentally in patients lacking a suitable stem cell donor [9,38,39].

Invasive candidiasis (IC) in CGD patients

IC is far less common than IA in this patient population. In the US registry of 368 CGD patients, *Candida* species were isolated from 20% of meningitis cases (most common cause), 11% of bacteraemia/fungaemia cases, and 7% of suppurative

adenitis cases. However, they were rarely (2%) isolated from patients with pneumonia or liver abscesses. IC was the cause of death in 4% of patients [13]. In the European cohort of 429 patients, *Candida* species were recovered from 3% of patients with septicaemia, 2% of those with pneumonia, <1% of liver abscesses, and 0.5% of lymphadenitis cases [14].

IFIs caused by other species in CGD patients

Among other fungi causing infection in these patients, *Paecilomyces* species have been most frequently reported, being the third most common cause of osteomyelitis in the US registry (8% of cases) [13]. *Paecilomyces variotii* is the *Paecilomyces* species commonly implicated, whereas *Paecilomyces lilacinus* has been rarely isolated. Besides osteomyelitis, *Paecilomyces* have been implicated in cases of pneumonia, soft tissue infection and abscess formation [40–43].

A number of other species also have been reported to cause IFIs in CGD patients, including members of the genera *Scedosporium*, *Trichosporon*, *Acremonium*, *Exophiala*, *Penicillium*, *Rhizopus*, *Absidia*, *Fusarium*, *Microascus*, *Inonotus*, *Chrysosporium*, *Cladophialophora*, *Neosartorya* and *Alternaria*. In the majority of these cases, IFIs have manifested as pneumonia, soft tissue infection or bone infection [8,13,44–55].

Other Phagocytic Disorders

Myeloperoxidase deficiency

Myeloperoxidase deficiency has a prevalence of one in 2000–4000 in Europe and the USA. Myeloperoxidase is produced in neutrophils and monocytes and released into the phagosomes, playing an adjunctive role in phagocytosis; its absence is associated with impaired killing of *Candida* species *in vitro* and in animal models. The vast majority of myeloperoxidase-deficient individuals are, however, asymptomatic [3,56,57]. The susceptibility to invasive *Candida* infections appears to be increased in the presence of other predisposing conditions, such as diabetes. Overall, IFIs occur in fewer than 5% of myeloperoxidase-deficient individuals. IC in these patients may present as candidaemia, disseminated infection, pneumonia, osteomyelitis, meningitis or liver abscess. Antifungal prophylaxis is not indicated [3,8,57–60].

Leukocyte adhesion deficiency (LAD)

LAD comprises a group of rare inherited disorders of leukocyte rolling, adhesion and cytoskeletal regulation [1]. Although older reviews concerning LAD patients suggested increased susceptibility to infections caused by *Candida* and *Aspergillus* species, there have been very few case reports of IFIs in these patients in recent years [3,8].

Congenital neutropenias

Patients with cyclic neutropenia are at low risk of IFIs, owing to the short duration of the neutropenia phase and the bone marrow's residual capacity to produce neutrophils when stimulated. Similarly, reports of IFIs among patients with other forms of congenital neutropenia (Kostmann syndrome, and neutropenias associated with metabolic or immunological disorders) are scarce in the literature [3,61,62].

Cellular and Combined Immunodeficiencies

Severe combined immunodeficiency (SCID)

An expanding group of distinct congenital immune defects, affecting both T-cell and B-cell function, is represented under the term SCID [1,2]. Increased susceptibility to fungal infections is observed among these patients. *Candida* and *Aspergillus* are the genera most commonly implicated in previous reports. IC may manifest as meningitis or pneumonia [63,64]; aspergillosis may present as lung infection [65,66]. Isolated cases involving other fungi, namely *Acremonium* and *Pichia* species, have also been published [67,68].

DiGeorge syndrome

Patients with DiGeorge syndrome have variably decreased T-cell numbers and, in the case of significant thymic hypoplasia or aplasia, they present with a SCID-like picture [1]. There are few reports of IA in these patients; it may manifest as lung or disseminated infection [69,70].

X-linked hyper-IgM syndrome

Patients with X-linked hyper-IgM syndrome have a combined cellular and humoral defect, and should be distinguished from those with the autosomal hyper-IgM syndrome, where cellular immunity is not affected [71]. Increased susceptibility to fungal infections has been observed in these patients, with *Candida*, *Cryptococcus* and *Histoplasma* being the genera most commonly implicated. IC may present as a bloodstream infection, and cryptococcosis as central nervous system, lymphonodular, bloodstream or disseminated disease [71–73]. Histoplasmosis may manifest as pneumonia, hepatitis or disseminated disease, involving the lungs, bone marrow and bloodstream [71,74].

Wiskott–Aldrich syndrome

The clinical course and infectious complications in patients with Wiskott–Aldrich syndrome are more severe in those with undetectable or truncated Wiskott–Aldrich syndrome protein (WASP) than in those with normal or reduced amounts of full-length mutated WASP. IFIs appear to affect

exclusively WASP-negative patients; in a series of 23 WASP-negative individuals, nine episodes of IC and three of aspergillosis were observed [1,75].

Humoral Immunodeficiencies

Common variable immunodeficiency (CVID)

Patients suffering from humoral immunodeficiencies (such as X-linked or autosomal recessive agammaglobulinaemia and IgA deficiency) do not generally exhibit increased susceptibility to fungal infections. CVID, however, comprises a heterogeneous group of disorders, which often include abnormalities in T-cell phenotype and function, secretion of cytokines, or T-cell receptor signalling events [1,64,76]. A number of case reports of IFIs in CVID patients have been published, including histoplasmosis (meningitis and disseminated infection), aspergillosis (lung infection and liver abscess) and disseminated infection caused by *Penicillium marneffei* [77–82].

Other Congenital Immunodeficiencies

Hyper-IgE syndrome (HIES)

HIES is characterized by elevated IgE and eosinophilia, eczema, and recurrent skin and pulmonary infections. The autosomal dominant (AD) form of HIES is further characterized by connective tissue and skeletal abnormalities (coarse facial features and retention of primary teeth) as well as disordered inflammation [83,84]. Recently, AD HIES was shown to result from mutations in the signal transducer and activator of transcription (STAT) 3 gene [85]. HIES patients display a distorted Th1/Th2 cytokine production pattern favouring Th2 responses, which is manifested by decreased production of IFN-γ in response to infectious stimuli (*S. aureus* and *Candida albicans*) [86–88]. In addition, a profound reduction in the number of Th17 cells has been recently described, and proposed to be one of the diagnostic features for HIES [89,90].

Increased susceptibility to IFIs has been reported for HIES patients, including yeast infections caused mainly by *Candida* species (bloodstream infection, disseminated disease, visceral candidiasis, endocarditis, and endophthalmitis) [91–94], *Cryptococcus neoformans* (meningitis and gastrointestinal disease) [95,96] and *Histoplasma capsulatum* (ileocecal histoplasmosis) [97]. *Aspergillus* species may also affect HIES patients, usually by colonizing pre-existing pneumatocoeles and forming aspergillomas. Occasionally, however, local invasion of the lung parenchyma may occur, and this can rarely be followed by dissemination to the central nervous system and formation of mycotic aneurysms [98–101]. In a series of 64 AD HIES patients, 28.1% developed mould infections caused by *Aspergillus* (n = 16) or *Scedosporium* (n = 2) species. The attributed mortality was 17%. Fungicidal activity and chemotaxis were not different between neutrophils from AD HIES patients and those from healthy controls. IFIs in HIES patients commonly occurred in their fourth decade of life. This late-onset risk of IFI despite normal phagocytic function was associated with bronchiectasis/pneumatocoeles, and was probably related to the role of STAT3 in lung epithelial homeostasis and defence [102].

Defects in the IFN-γ–IL-12 axis

A number of distinct defects in components of IL-12, the IL-12 receptor, IFN-γ receptor or STAT1 have been described [1,3]. Affected patients have been reported to develop disseminated infections caused by endemic fungi (*H. capsulatum* and *Paracoccidioides brasiliensis*) [103,104].

Conclusions

Patients with congenital phagocytic, cellular or combined immune defects exhibit increased susceptibility to IFIs. CGD and AD HIES are associated with the highest incidence of IFIs among congenital immunodeficiencies. Knowledge of the spectrum of implicated fungal pathogens and clinical presentation of IFIs in these patients, together with a high degree of suspicion, are essential for timely diagnosis. Uncommon species isolated from these individuals should not readily be discarded as contaminants. The limitations of newer diagnostic modalities (e.g. galactomannan antigen detection in CGD patients) should be taken into account. Administration of antifungal agents alone may not suffice for successful management of IFIs in patients with congenital immunodeficiencies. Surgical intervention is often necessary; adjunctive immunotherapy may be considered, although this has not been systematically studied. Prophylaxis with IFN-γ and itraconazole is recommended for CGD patients.

Transparency Declaration

The author has no conflicts of interest.

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