Candida perforation of the intestine in an HIV-exposed but uninfected infant

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Background. Oral and nappy *Candida* infections are common in neonates and infants, but candidaemia and its consequences are more often seen in children with risk factors for immunosuppression. This case presentation illustrates that exposure to HIV, without infection, should be considered one of those risk factors.
Objectives. To determine whether HIV-exposed, but uninfected, children have immune dysfunction that could alter their disease profile, and to elucidate the interactions of the gastrointestinal tract (GIT) with *Candida* infections.
Methods. Keywords/key phrases searched on databases were: candidiasis; GIT and *Candida*; HIV-exposed infants; immunity and HIV-exposed neonates.
Results. Several detailed original studies confirm an impaired immunological response in neonates and infants born to HIV-infected mothers. Impairment extends to children born to mothers on antiretroviral medication. The duration of immune dysfunction is unclear, but it appears to persist for several years. Homeostasis of the GIT is essential in order to prevent the translocation of *Candida* into the bloodstream. GIT immunity plays a critical role in the clearance of fungi. The HI virus interferes negatively with this ability.
Conclusion. If HIV-exposed but uninfected children have a degree of immunodeficiency, then the risk of opportunistic infections is higher than in HIV-unexposed uninfected children. The clinician should bear this in mind when these patients present, in order to decrease the morbidity and mortality associated with delayed diagnosis and treatment of candidaemia.

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Case study

A 7-month-old boy was admitted to hospital following a 5-day history of acute gastroenteritis. He was acidotic, septic and hypovolaemic. Broad-spectrum antibiotics were initiated and he was admitted to the intensive care unit. He also had severe nappy and oral candidiasis, which had been noted at a previous clinic visit. The mother was HIV-infected and had been on the prevention of mother-to-child transmission (PMTCT) programme. The patient was HIV-negative on routine polymerase chain reaction testing at 6 weeks and when tested again on admission. His clinical condition did not improve, and a few days after admission free air was demonstrated on the plain abdominal radiograph. At laparotomy, multiple focal jejunal perforations were noted. The rest of the bowel was inspected closely and appeared grossly normal with no signs of ischaemia or necrosis. The perforated intestine was resected and sent to the laboratory for testing. Histological examination of the bowel confirmed the presence of the hyphae of *Candida albicans*, which is the invasive form of candidiasis. Blood cultures conducted at the same time grew *C. albicans*, reflecting *Candida* fungaemia.

It is reasonable to consider that the *C. albicans* entered the bloodstream following translocation from the gastrointestinal tract (GIT). Once source control had been obtained by resecting the affected bowel segment and the offending organism had been identified, intravenous antifungal treatment (amphotericin B 1 mg/kg/day titrated against blood test results) was commenced and continued for 21 days. The oral and nappy candidiasis was treated topically with an antifungal agent. Clinical and biochemical improvement was rapid, and the infant survived to discharge from hospital.

Discussion

The arsenal of virulence factors that *Candida* has at its disposal, is the subject of intensive research. Of particular interest is its ability to shift between a commensal (yeast) state and a pathogenic (hyphae) state.[1] The events that govern these changes are not clearly understood. Exposure to HIV may play a role, by changing the environment in which the organism resides.

The HIV epidemic has added to a growing at-risk population,[2] and HIV-exposed uninfected (HEU) infants have demonstrated a higher risk of morbidity from infection than HIV-unexposed, uninfected (HUU) infants.[3] HEU infants had a 2.74 times (confidence interval 0.85 - 8.78) higher risk of hospitalisation than HUU infants in the first year of life.[3]

Suggested reasons for this phenomenon have included lowered immunity in the HEU infants, as demonstrated by a poorer antibody response to *Haemophilus influenzae* type B (Hib), pertussis, pneumococcus and tetanus vaccines.[4] Lower levels of specific and protective antibodies were identified in serum sampling of these patients.[4] In a second study, HEU infants had lower levels of naïve TCD4+ cells, higher B lymphocyte apoptotic levels, and changes in dendritic cells, which could potentially interfere with antigen presentation.[5] If the immune system cannot recognise the fungus, it cannot respond appropriately to the threat of disease. This is one reason why superficial infections may spread to other body sites instead of being contained, as would be expected in healthy immunocompetent individuals.[2]

Many studies have analysed maternal and neonatal immune function in both HEU and HUU population groups. HEU infants have demonstrated several immunological abnormalities.[6] The roots of poor immune responsiveness seem to stem from *in utero* responses, since proteins from the HI virus can pass across the placenta and have been suggested to be the main reason for the impaired progenitor cell function noted.[5] This is reflected by the alteration in lymphocyte number and function reported for exposed newborns.[5] Analysis of cord blood from infants with HIV-infected

mothers has revealed a reduction in interleukin-12 production, suggesting an immunosuppressive effect of *in utero* exposure to HIV.[7]

In utero exposure to highly active antiretroviral therapy (HAART) can modify the developing immune system and influence the immune response of infected neonates.[6] HAART appears to act on the placental environment, changing the expression of cytokines,[5,8] resulting in abnormal mitochondrial function[5] and maturation of T and B lymphocytes.[5,6] Fetal antiretroviral exposure was also associated with lowered immunoglobulin G levels.[9] This suggests an alteration in humoral responses due to exposure to a chronically activated maternal immune system.[9] The longer the duration of exposure to HAART, the higher the proportion of immature B cells in the blood of the newborn.[6] Therefore, despite lack of HIV infection in the neonate or infant, the immune system responds in an HIV-specific way, even when PMTCT exposure is operational.

These HIV-specific responses of the immune system persist to at least 6 months of age, but probably disappear by age 7.[7] A study that followed HEU children exposed to a PMTCT programme indicated that while total lymphocyte counts were not below levels for the definition of lymphopenia, they were demonstrably low.[10] $CD4^+$ counts were also reduced in the first year of life and $CD8^+$ counts remained low until 8 years of age.[10] This concept of delayed return to full immunity was also suggested in a study by Borges-Almeida *et al*.,[6] which demonstrated that while an abnormal peripheral blood count reverses fairly quickly, T-lymphocyte changes persist for as long as 8 years.[6] It is unclear what the full clinical significance of these immune changes are, or at what point the child's immune system reaches its full maturity. These studies imply the need for long-term follow-up of HEU children.

Having established that HEU neonates and infants have impaired immunity, it is necessary to consider what the implications might be at a gastrointestinal level.

It seems probable that the increase in the incidence of fungal infections is directly proportional, at least in part, to the increase in the population of immunocompromised individuals.[2] Research indicates that HEU infants should be included in this population group. Fungal infections of the skin, nappy area and oral mucosa are common.[11] Such infectious organisms may then spread from the GIT, since *Candida* is a normal gut commensal.[11,12] Children usually have a natural immunity to fungi,[2] which do not cause severe morbidity in healthy, non-hospitalised individuals whose immune system is able to identify and clear the fungal infection. Invasive fungal infections can however be lethal in immunocompromised individuals, who are especially susceptible to *C. albicans*, although non-albicans *Candida* species are becoming increasingly important pathogens.[2]

Factors that increase the risk of fungal infections commonly include admission to intensive care units, indwelling catheters, impaired immune function, long-term antibiotic use, prior bacteraemia, H2-receptor antagonist use, total parenteral nutrition, prematurity, extremely low birth weight, gastrointestinal congenital anomalies, major surgery, mechanical ventilation, dialysis and burns.[13-15]

As immunocompetent patients are at lower risk for invasive candidiasis than those who are immunocompromised, Hacimustafaoglu *et al.*[13] recommend that fungal prophylaxis should not be used in non-neonatal immunocompetent patients. To our knowledge the recent literature contains only two reports of gastrointestinal perforation secondary to *Candida* in immunocompetent children. One was a 3-year-old whose gastric ulcer perforated acutely.[16] Histological specimens and blood specimens cultured *C. troplicalis*.[16] The second case involved an 11-month-old who presented with a tender abdomen and protracted diarrhoea.[17] Subsequent to admission the child developed an intestinal perforation.[17] Histological and blood specimens cultured *C. albicans*.[17]

Candida becomes pathogenic when the gastrointestinal immune defences are compromised.[18] Changes in local conditions and immune responses result in mucosal disease, and this in turn increases the chance of invasive disease developing.[11] Only slight alterations are necessary in order for *Candida* to transform from a commensal organism to a pathogenic one.[18] For this reason, even superficial *Candida* infections should be regarded in a serious light when present in immunocompromised individuals.

Changes in immunocompromised individuals include immune and cellular interaction at a gastrointestinal level that affect the initiation of a systemic inflammatory cascade and clearance of a pathogen.

Gut-associated lymphoid tissue contains T and B cells and immunoglobulin A.[12] Differentiation and proliferation is stimulated when these cells interact with *C. albicans*.[12] A low concentration of immune cells is proportional to a weaker immune response.

When the *Candida*-mucosal epithelial cellular interaction is altered, under-stimulation of neutrophils (important in stimulating immune pathways and direct killing of fungi) and subsets of T and B cells, results.[11]

Production of pro-inflammatory cytokines and chemokines by the host cells in response to *C. albicans* plays a critical role in recruitment and activation of immune cells and final clearance of organisms.[18,19] T-helper lymphocytes play an integral role in defence against fungi.[12] Once activated, these cells produce pro-inflammatory cytokines.

Since the immune response plays such an important role in maintaining homeostasis, a decrease in the immune system's arsenal in HEU infants is an important consideration when treating superficial *Candida* infections. This is especially true when the infant presents with signs of systemic infection and a superficial candidiasis is also diagnosed. Perforation of the GIT is a natural progression of the invasive form of *Candida* infection, and this diagnosis should be higher up on the differential diagnosis list than it would be for an immunocompetent infant.

Conclusion

A growing body of evidence suggests that HEU neonates and infants are immune impaired when compared with HUU individuals – this is despite the use of PMTCT. It is also well established that gut-*Candida* interaction and local immunity play an important role in the establishment of invasive candidiasis. HEU children may already be at a disadvantage when encountering other illnesses that stress their already weakened immune system, and may have an increased risk of intestinal perforation from *C. albicans*. Superficial *Candida* infections are common, but in HEU infants they should be closely monitored and their resolution ensured, as they may be an external indicator of an internal process.

Further studies should be encouraged to determine whether *Candida* overgrowth of the GIT is associated with invasive disease in HEU patients, as opposed to a just a pathological change of the fungus in normal concentrations. These studies would guide treatment methods, determining whether options such as use of non-absorbable antifungals to eradicate *Candida* overgrowth in the GIT, should be utilised in HEU patients presenting with superficial *Candida* infection.[20]

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