III. DIARRHEAL DISEASE ASSOCIATED WITH HIV INFECTION AND AIDS

Introduction

Diarrheal disease is a common complication of HIV infection and AIDS, occurring in 30 to 50% of North American and European patients with AIDS and in more than 80% of African AIDS patients (Piot et al., 1984; Smith et al., 1992; Bartlett et al., 1992).

A salient feature of HIV-associated diarrheal disease among Africans is its recurrence and chronicity. Diarrhea of at least one month duration is seen in 40 to 80% of the AIDS patients.

In Zaire and Rwanda, studies by Colebunders et al. in 1987 and Clerinx et al. in 1993, revealed that respectively 84% and 94% of the subjects with chronic diarrhea were HIV-seropositive. Chronic diarrhea unavoidably leads to wasting; this association has been referred to as “slim disease” in Africa (Serwadda et al., 1985). When present in HIV-seropositive individuals an unexplained chronic diarrhoea-wasting complex meets the criteria of an AIDS-defining illness (WHO, 1986).

The frequency of the various enteric pathogens responsible for chronic diarrhoea in HIV-infected subjects greatly varies with the geographical sites where the observations are collected; it reflects not only variations in the prevalence of endemic infections resulting from differences in exposure to the pathogens, but also variations in the availability of technical facilities. This is illustrated in Table 1 below which reproduces the prevalence of enteric pathogens among HIV-seropositive patients with chronic diarrhea from various geographical areas.

There are three types of enteric infections that can affect the HIV-infected subject: .

a) The non-inflammatory type involves the small bowel and results from the action of an enterotoxin or a pathogenic process altering the absorptive function of the villi. It includes as enteric pathogens Cryptosporidium, Microsporidium, Isospora belli, Giardia intestinalis, Mycobacterium avium-intracellulare, Salmonella sp., Campylobacter sp. and several viruses;

b) The inflammatory type arises in the large bowel and results from an invasive process, toxin-mediated or not, caused by a range of micro-organisms including Shigella sp., Salmonella sp., Campylobacter sp., Clostridium difficile, Mycobacterium avium-intracellulare, E. histolytica, cytomegalovirus, adenovirus, herpes simplex virus;

c) The enteric fever type is characterized by early invasiveness of the Peyer’s patches and regional lymph nodes and production of a systemic infection. Salmonella sp. and Campylobacter sp. are predominantly involved in this type of diarrheal disease.

Table 1: Prevalence (%) of enteric pathogens in HIV-seropositive patients with chronic diarrhoea in Africa and USA

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Zaire</th>
<th>Uganda</th>
<th>Zaire</th>
<th>Central Africa Republic</th>
<th>Burundi</th>
<th>Zambia</th>
<th>Rwanda</th>
<th>USA</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>(n=46)</td>
<td>(n=23)</td>
<td>(n=106)</td>
<td>(n=105)</td>
<td>(n=100)</td>
<td>(n=44)</td>
<td>(n=81)</td>
<td>(n=43)</td>
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<tr>
<td>NO PATHOGEN</td>
<td>61</td>
<td>40</td>
<td>41</td>
<td>NA</td>
<td>NA</td>
<td>43</td>
<td>63</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>PARASTES</td>
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<td>19</td>
<td>13</td>
<td>7</td>
<td>0</td>
<td>15</td>
<td>16</td>
<td>NA</td>
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<tr>
<td>Cryptosporidium</td>
<td>22</td>
<td>9</td>
<td>0</td>
<td>NA</td>
<td>2</td>
<td>32</td>
<td>NA</td>
<td>14</td>
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<td>Isospora belli</td>
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<td>0</td>
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<td>10</td>
<td>6</td>
<td>NA</td>
<td>0</td>
<td></td>
<td></td>
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<td>Microsporidium</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>Giardia intestinalis</td>
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<td>10</td>
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<td>0</td>
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<td>E. histolytica</td>
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<td>0</td>
<td>10</td>
<td>6</td>
<td>NA</td>
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<td>Strongylodes stercolaris</td>
<td>4</td>
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<td>5</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BACTERIA</td>
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<td>4</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>23</td>
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<td>Shigella sp.</td>
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<td>NA</td>
<td>9</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Salmonella sp.</td>
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<td>3</td>
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<td>NA</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mycobacterium</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td></td>
<td></td>
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<tr>
<td>Aeromonas sp.</td>
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<tr>
<td>VIRUS</td>
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<td>0</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Henry et al. 1986
2. Serwankambo et al. 1987
3. Colebunders et al. 1988
4. Vohlo et al. 1988
5. Kadenye et al. 1989
6. Conlon et al. 1990
7. Clerinx et al. 1993
8. Greenson et al. 1991

NA: not available
1. Cryptosporidiosis is caused by Cryptosporidium, an intestinal protozoan measuring 5 to 6 microns in diameter and belonging to the same family as Isospora and Toxoplasma, infecting mainly the epithelial cells of the small intestine.

The disease may affect immuno-compromised as well as immuno-competent hosts. In profound immuno-deficient patients, it is characterized by watery diarrhoea with frequent and voluminous diarrhoeal stools, cramping, abdominal pain, weight loss, anorexia, malaise and low-grade or no fever. Dehydration, electrolyte imbalance and severe wasting resulting from high volume diarrhoea may require hospitalization. The parasite may also invade the respiratory and biliary tracts. Asymptomatic Cryptosporidium carriage occurs occasionally.

Definite diagnosis of the reinfection is established by demonstration of oocysts of the parasite in the stools or duodenal fluid. Oocysts are best identified by using acid-fast stains, for instance the Kinyoun or the auramin staining methods. As oocyst excration can be intermittent, several stool samples should be examined. Oocysts may also be identified in intestinal biopsy specimens.

The oocysts are resistant to numerous disinfectants and can persist unaltered for some time in the environment. Water-borne epidemics as well as person to person transmission have been described. Cryptosporidiosis is a common cause of diarrhoea in USA occurring in 10 to 20% of the AIDS patients and in up to 48% of the African AIDS patients (Sewankambo et al., 1987).

So far, no therapy has been effective. However, some success has been obtained with leptazuril and paramomycin, but further trials are warranted.

2. Isosporiosis diarrhoea is due to Isospora belli, a protozoan of 20 to 30 by 10 to 20 microns, mainly parasitizing the enterocytes of the small intestine and causing a severe and protracted watery diarrhoea. Clinically it cannot be differentiated from diarrhoea due to Cryptosporidium. The disease has been diagnosed in 1 to 3% of the AIDS patients in the USA and in up to 19% in Africans (Henry et al., 1986).

Diagnosis of isosporiosis relies on the demonstration of the parasite in the stools or in intestinal biopsy specimens using acid-fast staining techniques as for the screening of Cryptosporidium. Due to irregular excretion, several samples should be examined.

Isosporiosis responds well to high doses of trimethoprim-sulphamethoxazole. Recurrences may be prevented by a suppressive therapy with a lower regimen of the same drugs or with weekly sulphadoxine 500mg and pyrimethamine 25mg.

3. Microsporidiosis is a newly described protozoan infection caused by several microsporidia species, the best known being Enterocytozoon bieneusi.

Microsporidiosis has been detected in 14 to 33% of North American patients with AIDS and chronic diarrhoea. Due to the lack of facilities and systemic screening of the parasite, the prevalence of the disease in Africa remains unknown. However, microsporidiosis has been identified in Africa by Lucas et al. in 5 out of 77 (6.5%) duodenal and colon biopsies from Ugandan and Zambian AIDS patients (Sewankambo et al., 1987; Conlon et al., 1990).

Clinical manifestations are similar to those of cryptosporidiosis and isosporiosis. In heavily infected subjects, the epithelial cells may be necrotic with occasionally sloughing and disruption of the basement membrane.

Diagnosis was initially based on the finding of the parasite by electron microscopy of intestinal biopsy specimens but recently the use of special staining has allowed the detection of the parasite in the stools.

Marked reduction in diarrhoeal output in patients with microsporidiosis has been obtained with metronidazole and albendazole.

4. Mycobacterium avium intracellulare is considered as the most common cause of disseminated bacterial infection among AIDS patients in the USA.

The small intestine and the colon are both sites that may be affected by M. avium systemic infection, resulting clinically in chronic diarrhoea, abdominal pain, malabsorption and marked wasting. Histologically the infection should be differentiated from Whipple disease. M. avium is detectable in the stools by the use of acid-fast stains and by culture on appropriate media.

In the USA M. avium is estimated to produce disseminated infection in 40% of patients with AIDS and enteritis in up to 23%. In Africa the pathogenic role of M. avium in HIV-infected patients appears to be very limited (Colebunders et al., 1990; Conlon et al., 1989).

5. Several studies on Bacteria conducted in Europe and Africa have revealed only a modest contribution of the common enteric pathogens (Salmonella, Shigella and Campylobacter) to chronic diarrhoea.

However, in Kigali, systematic screening for bacterial pathogens by culture of three different stool samples and/or rectal swabs has been much rewarding, the yield being 23% for Shigella sp., 9% for Salmonella sp. and 2% for Campylobacter sp. In addition non-typhic Salmonella are the bacterial pathogens most often recovered from blood (Taelman et al., 1990). This explains that non-typhic Salmonella bacteraemia
representing 14.5% of all the AIDS cases is the third most frequent AIDS-defining illness in Kigali. Similar findings have been made in Kenya (Gilks et al., 1990).

Bacterial infection, more particularly with *Shigella* and *Salmonella*, do often not respond to the common antibiotics and require treatment with quinolones or cephalosporines, both costly drugs for resource-poor countries. In addition recurrences are quite frequent.

*Clostridium difficile* toxin has been found in 25 out of 200 (12.5%) of AIDS patients with diarrhoea studied in USA. A majority of them had taken antibiotics. Due to the difficulty of performing assays of the toxin nothing is known about the possible role of this microorganism.

6. *Cytomegalovirus* (CMV) may involve any part of the gastrointestinal tract. When it infects the intestine it may cause chronic disease but also occasionally gangrenous bowel intestinal perforation, toxic mega-

colon or ulcer. Histologically these findings correspond to CMV vasculitis. Whereas in the USA, cytomegalovirus enteric disease seems to occur with a frequency up to 35% (Greenston et al., 1991), in AIDS patients in Africa it has seldom been documented.

Other viruses (adenovirus, rotavirus) have been detected in HIV-infected patients with diarrhoea in the USA (Bartlett et al., 1992) and in Zaire (Thea et al., 1993); but no conclusive causal relation has been established between these viruses and diarrhoea.

7. Other micro-organisms prevailing in the tropics like *Entamoeba histolytica*, *Giardia intestinalis* and *Strongyloides stercoralis* have occasionally been found associated with chronic diarrhoea in HIV-infected patients but not significantly more often than in HIV-seronegative individuals.

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