

ORIGINAL RESEARCH

Enteric viral infections as a cause of diarrhoea in the acquired immunodeficiency syndrome

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Background and aims

The role of non-cytomegalovirus (CMV) enteric viral infection in causing diarrhoea in patients with human immunodeficiency virus (HIV) is poorly understood. We aimed to investigate the prevalence of these infections in acute and chronic diarrhoea.

Methods

Stool specimens from 377 HIV-infected patients presenting with diarrhoea were studied prospectively for evidence of non-CMV enteric viral infection. Patients with diarrhoea underwent investigation for gastrointestinal pathogens, including electron microscopic examination of stool for enteric viruses. We collected data on patients in whom enteric virus was identified and examined the association of enteric virus infection with diarrhoeal symptomatology.

Results

Eighty-nine (10.3%) stool specimens from 60 (15.9%) HIV^+ individuals were positive for coronavirus ($n = 13$, 22%), rotavirus ($n = 11$, 18%), adenovirus ($n = 30$, 50%) and small round structured viruses ($n = 5$, 8%) or dual infection ($n = 2$, 3%). Thirty-four of 52 (65%) patients available for analysis had acute diarrhoea, and 18/52 (35%) had chronic diarrhoea. Twenty-three of 52 (44%) patients had a concurrent gut pathogen. After exclusion of concurrent pathogens enteric viral infections were found to be significantly associated with acute as opposed to chronic diarrhoea ($P = 0.004$). The presence of adenovirus colitis was significantly more likely to be associated with chronic diarrhoea (15/21 cases) than adenovirus isolated from stool alone (9/23 cases) ($P = 0.03$). There was a trend towards an association between adenovirus colitis and colonic cytomegalovirus infection ($P = 0.06$).

Conclusion

Enteric viral infection is strongly associated with acute diarrhoea in patients with HIV. Light microscopic examination of large bowel biopsies can identify adenovirus colitis which is significantly associated with chronic diarrhoea, and in addition may facilitate gastrointestinal co-infection with CMV.

Key words: adenovirus, colitis, diarrhoea, electron microscopy, enteric virus, HIV

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Introduction

Despite the introduction of highly active antiretroviral therapy (HAART), diarrhoea remains a common manifestation of disease related to human immunodeficiency virus (HIV) infection and can be a diagnostic problem. Opportunistic infections of the gastrointestinal tract are responsible for 68–85% of both acute and chronic cases of diarrhoea in HIV-infected patients [1–3]. The principle opportunistic pathogens include cryptosporidia, microsporidia, mycobacteria and cytomegalovirus in addition to conventional pathogens found in the immunocompetent. Gut autonomic neuropathy [4], bacterial overgrowth [5,6] or HIV enteropathy [7] may account for a small proportion of the remaining so called 'pathogen-negative' cases of diarrhoea.

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Non-cytomegalovirus (CMV) enteric viral infections are likely to account for a significant proportion of pathogen-negative diarrhoea in HIV patients. Enteric viral infection has been increasingly recognized as a cause of both endemic and epidemic diarrhoeal disease [8,9]. Rotavirus, adenovirus and coxsackie virus have been implicated as causative agents of diarrhoea in primary immunodeficiency disease [10] and in immunosuppressed bone marrow recipients [11]. Adenovirus has been reported as a disseminated infection in AIDS and isolated from brain, lung and liver samples. However, the main manifestations of this infection appear to be in the gastrointestinal tract [12], where this and other enteric viruses can be isolated from the stool and intestinal tissue. Clear consensus about the role of enteric viruses in acute and chronic infection in HIV patients does not exist [13–18]. Few data exist regarding the natural history of these infections and their possible association with other pathogens. Adenovirus infection of colonic tissue has been described [19,20], but it is unclear whether 'adenovirus colitis' is responsible for symptoms in this group of patients.

We prospectively examined stool, dudenal, rectal and colonic biopsy specimens of 377 HIV^+ patients presenting with diarrhoea at our unit over a 30-month period for evidence of enteric viral infection. Prevalence, $CD4^+$ cell counts at which infection occurred and relationship to symptoms of diarrhoea were determined.

Methods

Patient selection and investigation

From June 1991 to December 1994, all patients attending the dedicated HIV out-patient clinic and in-patients at the Chelsea and Westminster Hospital who presented with diarrhoea were entered for the study. Diarrhoea was defined as the passage of more than three fluid stools per day. Chronic diarrhoea was defined as persistence of these symptoms beyond 4 weeks. All patients had stool specimens collected for the identification of enteric viruses by electron microscopy, and other enteropathogens (see below) by stool culture and microscopy.

Patients were reviewed as part of their normal clinical follow-up at least monthly and assessed for frequency and duration of symptoms. The decision to proceed to endoscopic biopsy of the duodenum, rectum or colon was based on clinical grounds, in particular the failure of stool analysis to provide a diagnosis or the severity of symptoms.

Symptoms were assigned as related to virus shedding if they occurred within a 2-week period of virus isolation or the diagnostic biopsy. In cases where there was prolonged virus shedding, the first positive sample was taken as the index sample. Patients in whom non-CMV enteric viruses were identified were defined as being co-infected if other gut infection (as defined below) was present at the time of viral isolation, or within 2 months prior to, or up to 1 month following viral isolation. Cases with microsporidia or cryptosporidia were considered to be co-infected even if the diagnosis was made prior to this 2-month period. CD4 cell counts measured by flow cytometry were taken within 2 months of viral isolation.

Microbiological diagnosis

Stool culture and microscopy

A standard protocol was adopted for analysis of stool specimens and has been reported in detail previously [21]. Briefly, stool specimens were cultured for *Mycobacteria*, *Salmonella*, *Shigella*, *Campylobacter*, *Aeromonas, Yersinia* and *Clostridium difficile* and in addition cytotoxicity assay for *C. difficile* was performed. Stool microscopy was performed using appropriate staining to identify *Cryptosporidium parvum*, *Microsporidia*, *Isospora belli* and *Giardia lamblia*.

Enteric viral identification by electron microscopy

At least two stool samples for virological examination were examined by electron microscopy. Samples were emulsified in a phosphate-buffered saline clarified in a bench centrifuge and the supernatant spun in an ultracentrifuge at 45 000 r.p.m. for 45 min and the pellet resuspended. The concentrated specimens were negatively stained with phosphotungstic acid before being placed on a carbon/Formvar grid and examined by electron microscopy.

Histology of mucosal specimens

Biopsies were taken from the distal duodenum, rectum and colon and were stained with haematoxylin and eosin (H&E), PAS and Ziehl–Nielsen and examined by light microscopy. Biopsies were also examined by electron microscopy. H&E and specific CMV immunoperoxidase staining were used to identify CMV infection of the duodenum, rectum and colon. At least three distal duodenal, rectal or colonic biopsies were obtained by upper gastrointestinal endoscopy, rigid sigmoidoscopy or colonoscopy. Biopsies (duodenal/rectal) were performed in 69% of the patients. Immunocytochemistry for adenovirus was performed with adenovirus primary antibody (Serotec no. MCA 489) [20]. Histological records of patients positive for adenovirus colitis were reviewed retrospectively. The histological characteristics

Table 1 Characteristics of patients with enteric virus present in stool

	Adenovirus	Coronavirus	Rotavirus	SRSV
n	27	11	9	5
Prevalence (%)	72	2.9	2.4	13
CD4	10	100	9	90
cells/ml*	(2–620)	(20–648)	(4–360)	(9–462)
HIV duration (years)	4 (1–10)	6 (1–11)	4 (3–8)	4.5 (3–8)
AIDS diagnosis (%)	22 (81)	4 (36)	6 (67)	3 (60)
Concurrent gut (%) pathogen	13 (48)	5 (45)	4 (44)	1 (20)
Acute diarrhoea (%)	16 (59)	8 (73)	6 (67)	>4 (80)
Concurrent gut pathogen	5	3	1	0
Chronic diarrhoea (%)	11(41)	3 (27)	3 (23)	1 (20)
Concurrent gut pathogen	8	2	3	1

Values for CD4 count and HIV duration given as median (range). *$P = 0.0007$.

of adenovirus colitis have been described previously [19,20].

Statistics

Non-parametric statistics were used unless otherwise stated using Kruskal–Wallis and Mantel–Haenzel χ^2. Data were analysed using Epi-Info software package.

Results

Prevalence of enteric virus in stool

Eight hundred and sixty-two stool samples from 377 individuals were examined during the 30-month study period. Eighty-nine stools were positive for enteric viruses from 60 HIV^+ individuals giving an overall prevalence of 15.9% [60/377]. Of these individuals, 13 were positive for coronavirus (22%), 30 were adenovirus (50%), 11 were rotavirus (18%) and five were small round structured viruses (SRSV) (8%). Two patients had a dual infection (adenovirus/rotavirus). Six cases were unavailable for analysis, thus a total of 52 cases with evidence of a single enteric virus in the stool were subsequently analysed. All but three of the available cases were homosexual males (two heterosexual males, one heterosexual female).

Characteristics of patients with enteric virus present in stool

Table 1 illustrates the case characteristics of the patients with rotavirus, adenovirus, coronavirus and SRSV infections. There was no significant difference in age, duration of known HIV infection or the use of antiviral (aciclovir, ganciclovir or foscarnet) and antiretroviral agents between the groups. However, median CD4 counts differed significantly in patients with adenovirus and rotavirus having substantially lower values at 10 and 9 cells/μl, respectively, in comparison to coronavirus, 100 cells/μl and SRSV, 90 cells/μl ($P = 0.007$). In keeping with this finding, the frequency of an AIDS (CDC IV) diagnosis was greater in those patients with adenovirus infections as opposed to coronavirus infections at 81% and 36%, respectively, although this did not reach statistical significance.

Co-infection and diarrhoea

A concurrent gut pathogen was found in 23/52 (44%) cases. Acute diarrhoea of less than 4 weeks duration' occurred in 34/52 (65%) of cases overall while chronic diarrhoea occurred in the remaining 18/52 (35%) cases. Those patients with concurrent gut pathogens were more likely to have chronic diarrhoea: 14/18 (78%) of those with chronic diarrhoea were positive for gut pathogens compared to 9/34 (26%) of the acute diarrhoea group ($P = 0.004$, 95% odds ratio (OR) 2.9 [1,2,4,7]). The co-pathogens present were cryptosporidia ($n = 7$), microsporidia ($n = 8$), other protozoa ($n = 7$), CMV upper gut ($n = 3$), CMV colitis ($n = 2$) and *Mycobacterium avium intracellulare* (MAI) of the gut ($n = 2$). None of the patients had cultures positive for bacterial pathogens. After exclusion of concurrent gut pathogens 25/29 (86%) patients had acute diarrhoea (11 adenovirus, five coronavirus, five rotavirus and four SRSV).

Comparison of patients with adenovirus colitis and stool carriage

Twenty-seven patients had adenovirus found in stool, of whom 13 had rectal biopsies performed. Four of these 13 biopsies had evidence of adenovirus in biopsy tissue (31%). In order to compare the pattern of infection in patients with

Table 2 Comparison between patients with adenovirus stool carriage and adenovirus colitis

	Adenovirus colitis	Adenovirus in stool
n	21	23
Rectal biopsy	21	13
Age (years)	37 (25–59)	38 (26–59)
CD4 cells/μl	20 (2–201)	10 (2–620)
AIDS diagnosis	18	19
Antiviral therapy	12	11
Antiretroviral therapy	11	6
Concurrent gut pathogen	10	12
Acute diarrhoea	6	14*

No significant differences, except *$P = 0.03$ (Fisher's exact test). Values for age and CD4 given as median (range).

adenovirus present in colonic mucosa with those who had adenovirus in stool only, histological records were reviewed retrospectively for additional cases with evidence of colorectal adenovirus infection; 21 cases were identified. The histological appearances of adenovirus infection of the large bowel have been described previously [19,20]. Table 2 illustrates the characteristics of these two patient groups. There were no significant differences in age, median CD4 counts, frequency of concurrent gut pathogens, AIDS diagnoses, antiviral or antiretroviral use between the groups. Fourteen of 23 (61%) cases in whom adenovirus was identified only in the stool had acute symptoms compared with 6/21 (29%) of individuals with histological evidence of colorectal adenovirus infection, the remainder having chronic diarrhoea ($P = 0.03$). This relationship persisted after stratification for presence of concurrent gut pathogens. Thus, patients in whom virus was isolated from the stool alone had an increased frequency of acute diarrhoea while patients in whom histological evidence of adenovirus infection was found were more likely to have chronic diarrhoea (OR; adenovirus colitis for acute diarrhoea 0.14 (95% CI 0.03–0.72)).

Repeat rectal biopsies were performed on 10 patients with histological evidence of colorectal adenovirus infection at a mean of 21 weeks after the original biopsy. In five cases there was evidence of persistent adenovirus infection; 13/20 duodenal biopsies performed at the same time as the definitive rectal biopsy were normal and no histological evidence of adenovirus infection was found in any of the duodenal specimens.

Co-pathogens in patients with adenovirus infection

The co-pathogens in the group of patients with histological evidence of large bowel adenovirus infection were: microsporidia (2), microsporidia and cryptosporidia (1), microsporidia and MAI (1), cryptosporidia (1), CMV colitis (3), CMV colitis and microsporidia (1) and other protozoa (1). A further four cases of CMV colitis were subsequently diagnosed. Thus, a total of eight of 21 cases of CMV colitis were identified among patients with histological evidence of colorectal adenovirus infection during the study period. Among patients in whom adenovirus was found in the stool alone only one of 13 cases who had undergone rectal biopsy had CMV colitis and there were no subsequent diagnoses of CMV colitis [1/13] ($P = 0.056$, Fisher's exact test).

Discussion

In this study we have found a 15.9% prevalence [60/377] of non-CMV enteric viral infection among HIV patients with diarrhoea. The prevalence of adenovirus was 7.2%, rotavirus 2.4%, coronavirus 2.9% and SRSV 1.3% of the 377 patients studied. After exclusion of concurrent pathogens non-CMV enteric viral infection was found to be significantly associated with acute as opposed to chronic diarrhoea ($P = 0.004$). Adenovirus and rotavirus infection occurred at significantly lower CD4 counts than either coronavirus or SRSV ($P = 0.007$). In patients with histological evidence of large bowel adenovirus infection (adenovirus colitis) chronic diarrhoea was significantly more common than in those in whom it was isolated in stool ($P = 0.03$). There was a trend towards an association between the presence of CMV colitis and adenovirus colitis ($P = 0.06$).

Prevalence rates for enteric viral infections in HIV patients vary widely between published studies from 6% to 54% [2,10,11,13–18]. These differences may be explained by geographical variations, discrepancies in detection rates between various methods and population sizes studied. The overall prevalence of enteric viruses in this study (15.9%) is similar to that of Schmidt *et al.* [18], who found an overall prevalence of 17% (6.6% adenovirus) using electron microscopy in a similar cohort of patients. Reverse-transcriptase polymerase chain reaction techniques are becoming available for the detection of some enteric viruses and are likely to be more sensitive than the electron microscopic techniques employed in this study. True prevalence rates may therefore be higher than those determined in this study.

The pathogenic role of enteric viral infection in HIV-related diarrhoea remains unclear. Using a previously validated investigative protocol to identify co-infection with known pathogens [21] we found that 25/29 (86%) of unselected HIV patients with enteric virus infection had associated acute diarrhoeal episodes (less than 4 weeks'

duration). In contrast, the presence of a concurrent gut pathogen known to cause diarrhoeal symptoms in the immunosuppressed was associated with chronic diarrhoea ($P = 0.004$). Data on viral carriage in asymptomatic patients in our study population are not available and we cannot therefore be certain of a causal role of these viruses in HIV-related diarrhoea. We also have reservations about the accuracy of analysis of formed stool. However, the strong association between acute diarrhoea and the presence of enteric viruses without evidence of other pathogens suggests this association. Three previous studies have suggested an association between enteric viral carriage and diarrhoea [13,14,18]. In other studies no association has been found [16,19,22], which may be explained in part by their focus on chronic diarrhoea as opposed to acute diarrhoea. Establishing a pathogenic role for enteric viruses in HIV-related diarrhoea is likely to remain difficult, in view of the occurrence of asymptomatic shedding of virus and the high rate of concurrent enteric pathogens in this group of patients, particularly those with chronic diarrhoea.

Both adenovirus and rotavirus were found to occur at significantly lower CD4 counts (10 and 9 cells/μl, respectively) than coronavirus and SRSV (100 and 90 cells/μl, respectively) ($P = 0.007$). This is in contrast with a previous report in which adenovirus and coronavirus infections were found to occur at similar median CD4 counts (20 and 67 cells/μl, respectively) [18]. Several other studies have found evidence of increasing prevalence of enteric viral infection with increasing immunosuppression [14–16,23]. The significance of this difference in susceptibility to adenovirus and rotavirus at lower CD4 counts and its relationship to pathogenicity is unclear.

Four patients of 13 (31%) in whom adenovirus was present in stool who also had a rectal biopsy were found to have evidence of adenovirus in the mucosa. This condition has been termed 'adenovirus colitis' and is poorly understood, with published material limited to case reports [19,20]. The clinical significance of adenovirus colitis has not been established. We therefore compared cases of adenovirus colitis identified from histological records with those in whom adenovirus was identified in stool. Cases were matched for CD4 counts, antiviral therapy and the presence of concurrent gut pathogens. In the adenovirus/stool group 14/23 patients had acute diarrhoea compared to 6/21 in the adenovirus colitis group ($P = 0.03$). There is a potential bias towards a rectal biopsy in patients with chronic diarrhoea and hence a diagnosis of adenovirus colitis. These results suggest that a proportion of patients develop overt mucosal inflammation in association with adenovirus infection and may go on to develop chronic diarrhoea. Further work is required to characterize adenovirus isolates from patients with adenovirus colitis. Subgenus F serotype 40 adenovirus has been associated with symptomatic gastrointestinal infection, and data from a seroprevalence study suggest the recently proposed adenovirus serotypes 48 and 49 may be endemic among gay men and sexual transmission is the likely source of exposure [24,25].

A further cause of chronic diarrhoeal symptoms in adenovirus infection may be an association with cytomegalovirus infection. We found that 8/21 patients with adenovirus colitis had or subsequently developed CMV infection in the colon, compared to 1/13 patients with adenovirus in stool alone (negative biopsies for adenovirus colitis) $P = 0.05$. Adenovirus infection has previously been associated with increased frequency of co-infections [18] and a facilitator role for the virus has been suggested [26]. We postulate that the cytopathic damage to the colonic epithelium caused by adenovirus, which may be extensive, may predispose to CMV infection. Additionally, adenovirus protein products have been shown to prevent killing by cytotoxic T cells, perhaps further inhibiting viral clearance [27]. However, this association remains speculative and further work is needed to establish the link.

Given the absence of histological evidence of adenovirus infection in patients in whom adenovirus was identified in stool, the source of virus remains unclear. We found no evidence of adenovirus in duodenal biopsies, consistent with a previous report [20]. Presumably, patchy transient infection of the epithelium elsewhere in the gut can be cleared even in these severely immunocompromised patients, as illustrated by the acute, self-limiting nature of symptoms in the majority cases. In a subgroup of patients with adenovirus, however, established rectal or colonic infection may occur and lead to impaired fluid absorption and hence chronic diarrhoea. Further studies are required to confirm the pathogenic role of the enteric viruses described and the impact of HAART on their occurrence.

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