Effect of concomitant HIV infection on presentation and outcome of rotavirus gastroenteritis in Malawian children


Summary

Background Rotaviruses represent important causes of severe diarrhoea in early childhood. We examined the effect of HIV infection on the presentation and outcome of rotavirus gastroenteritis in Malawian children.

Methods Children younger than 5 years who were treated for acute gastroenteritis at the Queen Elizabeth Central Hospital in Blantyre from July 1, 1997, to June 30, 1999, were enrolled. Children with rotavirus diarrhoea, with and without HIV infection, were followed up for up to 4 weeks after hospital discharge. Rotavirus disease severity (assessed with a 1/10 scale), duration of rotavirus shedding, and seroresponse to rotavirus were compared between HIV-infected and HIV-uninfected children.

Findings 796 inpatients (median age 8 months, 271 [34%] of whom were HIV-infected) and 400 outpatients (median age 65 [16%] of whom were HIV-infected) and 400 outpatients (median age 8 months, 65 [16%] of whom were HIV-infected) were enrolled. Children with rotavirus diarrhoea, with and without HIV infection, were followed up for up to 4 weeks after hospital discharge. Rotavirus disease severity (assessed with a 1/10 scale), duration of rotavirus shedding, and seroresponse to rotavirus were compared between HIV-infected and HIV-uninfected children.

Conclusions Malawian children with concomitant HIV infection manifested acute rotavirus infections. Rotavirus vaccine safety and immunogenicity in HIV-infected infants should now be re-evaluated.

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Introduction

Rotaviruses are the main cause of severe, dehydrating diarrhoea in infants and young children throughout the world. By contrast, with more-developed countries, in which rotavirus causes few deaths (<40 per year in the USA), an estimated 500 000 to 870 000 deaths annually are caused by rotavirus infection in low-income countries. Consequently, the development, testing, and introduction of rotavirus vaccines is a public-health priority. Early rotavirus vaccines seemed to be less effective in tropical settings, but newer vaccines have shown similar levels of protection (90-100%) against the most severe outcomes of rotavirus infection in more-developed and less-developed countries.

Infection with HIV is common among children in many countries in sub-Saharan Africa, and diarrhoeal disease is a leading cause of illness and death in HIV-infected children in these areas. Although co-infections with rotavirus and HIV have been identified in HIV-endemic areas, no studies have described the outcome of rotavirus gastroenteritis in HIV-infected children. Rotavirus infections in other groups of immunocompromised children (eg, infants with congenital immunoodeficiency syndromes) can result in severe, prolonged, life-threatening diarrhea, with fatal virus excretion persisting for many months, and reinfections with rotavirus have been reported in immunocompromised children.

Most rotavirus vaccines in development include live, oral, attenuated strains, and concerns exist regarding their use in infants who might be immunocompromised. Specifically, the US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommended that the (now suspended) tetranivalent human-reovirus-like rotavirus vaccine should not be given to infants born to HIV-infected mothers (unless HIV infection in the infant has been excluded), and suggested further research in this area. Understanding the behaviour of natural rotavirus infection in HIV-infected children is an important first step in this process. We therefore undertook a 2-year study of rotavirus infections in Blantyre, Malawi, where mother-to-infant transmission of HIV contributes substantially to high levels of early childhood mortality. The objectives of this study were to examine the effect of host HIV infection on the severity of rotavirus disease, and on the duration of faecal shedding of rotavirus and the serum immune response to rotavirus infection. We wished to test the hypothesis that concomitant HIV infection increases the severity of rotavirus disease and delays the faecal clearance of rotavirus and diminishes the serum immune response.

Methods

Participants The study was carried out from July 1, 1997, to June 30, 1999, at the Queen Elizabeth Central Hospital (QECH), Blantyre, Malawi, which is the largest city in the Southern Region of Malawi, and has a population of about one million.
outcome over time and in different geographic regions. Second, a reliable culture method for P. carinii and a subsequent in-vivo model for assessment of drug susceptibility need to be developed. Thus, our speculation of another mutation, in combination with the known DHPS mutations that might confer clinically significant drug resistance, suggests that mutations should be sought in other gene targets. Fourth, assessment of drug resistance in P. carinii will be facilitated by development of standardised definitions of treatment outcome. Finally, a larger, multicentre study should be sought in other gene targets. Fourth, the known DNA sequencing, nested by Laurence Huang, Jane Carter, and David Rimland were members of the protocol development team. Charles Beard directed the members of the protocol development team. Charles Beard directed the

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References


negative group (11 of 50 [22%] vs 0 of 61, p=0.0001). Death after hospital discharge was often preceded by fever, respiratory symptoms, diarrhea, and poor feeding. Acute (enrolment) CD4 counts were significantly lower among HIV-infected children who died during follow-up (median 285 /μL [range 33–677]) than in those who completed follow-up (839 /μL [39–227]), p=0.005.

Of the 74 children who completed at least 3 weeks of follow-up (figure), a greater proportion of HIV-infected children than HIV-negative children shed virus after hospital discharge (table 3). Overall, 56 (76%) children had a four-fold rise in either IgG or IgA against rotavirus between acute and convalescent serum samples. The proportion of children who seroconverted did not vary by HIV status, and there was no difference between the ratio of acute to convalescent titres between HIV-infected and HIV-uninfected children (table 3). There was no difference in the fates of shedding or seroresponse by age, sex, WAZ score, CD4 count, CD4/CD8 ratio, severity of illness, or rotavirus strain type (data not shown).

Discussion
In this 2-year hospital-based study of rotavirus gastroenteritis, we found that rotavirus was less common among HIV-infected children than among HIV-negative children. In those with HIV infection, the contribution of rotavirus might have been diluted by the effect of other enteropathogens—eg, parasites, bacteria, and perhaps viruses such as astroviruses and picobirnaviruses, which have been associated with diarrhea in HIV-infected adults.10 Although infection with HIV did not result in a younger age of presentation with rotavirus diarrhea, more than a third of cases overall were identified in children younger than 6 months. These data suggest that future rotavirus vaccine programmes in Malawi will need to provide adequate protection in this youngest age group.

We were unable to find significant differences in the clinical severity of rotavirus diarrhea between hospitalised children with and without HIV infection. However, significantly more deaths occurred during follow-up after hospital discharge among HIV-infected children than among HIV-negative children, and death was related to low CD4 count on presentation. Since the
precise causes of death in these children were unknown, whether the higher mortality in the HIV-infected group was caused by rotavirus or by an underlying HIV-disease complex could not be determined. In this study, some evidence of greater rotavirus disease severity among malnourished children was found. However, after controlling for age and HIV status, we found no effect of the WAZ score or the severity of rotavirus diarrhea.

HIV-infected children were more likely than HIV-negative children to shed rotavirus during follow-up, but in rotavirus-positive children, outcome was associated with diarrhea, and the clinical significance of this finding is questionable. Moreover, three-quarters of children showed a four-fold seroreversion to rotavirus after acute infection, and response rates did not differ by HIV status. The host factors necessary for rotavirus clearance in some children are unknown, but in mice, cell-mediated and humoral immune mechanisms have a role in the control of rotavirus infection. Presumably, at least one of these mechanisms is sufficiently conserved in the small intestinal mucosa of HIV-infected children to enable viral clearance, despite systemic evidence of immunodeficiency.

We found that children infected with P[6],G8 strains were significantly younger than those infected with other commonly identified strains. Unusual VP4 types (especially type P[6]) are well described in association with rotavirus infections of neonates, and a higher prevalence among older children of serotype G9 and a low rate of acquired neutralizing immune antibody to the VP7 and VP4 proteins of this strain might render young infants more susceptible to infection. In hospitalised children, from whom prospective clinical data were collected, we found that the severity score did not differ for the strain type. Although convincing evidence is lacking that severe diarrhoeal illness varies by strain, a study from Bangladesh found that rotavirus strains P2 and G3 were associated with the most severe dehydration but this finding did not seem to be of major clinical importance.

The findings of this study, taken together with those of smaller cross-sectional and longitudinal studies, suggest that rotavirus is not an opportunistic pathogen in children with HIV infection. However, despite the large number of children screened, only a small number of individuals completed follow-ups, and the power of this study to detect small differences in the duration of rotavirus shedding and seroresponse by HIV status is therefore limited. Although we cannot exclude the possibility of selection bias resulting from the high loss to follow-up through death and failure to complete the study, we did not attempt to detect viral RNA by RT-PCR, which might have underestimated the rate and duration of rotavirus shedding. By RT-PCR, Richardson and colleagues showed that 10% of healthy children admitted to hospital with severe rotavirus diarrhoea, a severe illness, shed viral RNA in stool for more than 20 days. The duration of diarrhoea is a measure of an inability to control these infections, and evidence of viral shedding indicates a need for more intensive diarrhoea, a severe illness, a focus for the study of children with HIV infection. With this focus, the large number of children screened, only 1.1% of healthy children were shedding rotavirus, and the duration of shedding was similar to that found in other studies. The finding of more frequent shedding among HIV-infected children during short-term follow-up after rotavirus infection requires further study, including assessment of the effect of rotavirus on HIV replication. The observation of clinically ineptaneous prolonged shedding in some HIV-infected children merits further investigation, and would be addressed in a large, longitudinal study with long-term follow-up.

In conclusion, rotavirus was detected less frequently among HIV-infected children, who were able to clinically resolve rotavirus infection irrespective of their immune status, and the effect of enteric rotavirus infection on HIV replication remains to be addressed. A higher proportion of HIV-infected than uninfected children were malnourished in this study, and there is some evidence of greater rotavirus disease severity among malnourished children. However, after controlling for age and HIV status, we found no effect of the WAZ score or the severity of rotavirus diarrhea.

Contributors

Nigel Costiloe, Ihsan Goubran, Stephen Graham, Robin Broadhead, Malcolm Molyneux, and Constance Magola were responsible for study design; Nigel Costiloe, Ihsan Goubran, Stephen Graham, and Helen Mcheson supervised the collection of clinical data and samples; Colin Kirkwood did the statistical analysis; and Gary Voller prepared the review and HIV ELISA assays. Nigel Costiloe wrote the paper with major contributions from I. Anthony Hart and Malcolm Molyneux.
A 48-year-old man was admitted with back pain and swelling. He had a history of angina, hypertension, right renal artery stenosis, and an elective abdominal aortic aneurysm repair in 1991. Three weeks before admission, he had undergone coronary angiography following an uncomplicated inferior myocardial infarct. Angiography had shown complete occlusion of the right coronary artery, a normal left coronary artery, and an estimated left ventricular ejection fraction of 50% with a left ventricular end-diastolic pressure of 9 mm Hg. At the time of his infarct his renal function was impaired, but comparable to that recorded in 1997 (creatinine 187 mmol/L). His renal function deteriorated transiently following angiography (urea 32 mmol/L, creatinine 546 mmol/L) but improved after 48 hours of intravenous fluids (urea 25 mmol/L, creatinine 450 mmol/L). He was then discharged and outpatient follow-up was arranged. On this admission he had no (cerebral) infarction and renal function had deteriorated substantially with a urea of 36 mmol/L and creatinine of 998 mmol/L. He was taking furosemide 40 mg daily, magnesium 75 mg daily, dilbrium 180 mg twice daily, aspirin 50 mg daily, ramipril 5 mg daily, and calcium carbonate 400 mg daily.

Two further episodes occurred, each resolving spontaneously within hours without specific treatment. There is usually a degree of renal impairment and a history of hypertension. A haemodynamically significant unilateral stenosis increases renin secretion from the juxtaglomerular apparatus, causing sodium and water retention by the contralateral kidney. A normal contralateral kidney suppresses its renin secretion and a renovascular stenosis, requiring intravascular volume. If there is bilateral renal artery stenosis, or an abnormal contralateral kidney this does not happen and volume overloading can occur. Renal artery stenosis can be treated by PTCA or surgical revascularisation.

References

The presence of unilateral or bilateral obstructive renal artery stenosis is a major cause of acute pulmonary oedema. Most patients have co-morbid cardiovascular disease and a renovascular aetiology is overlooked. Flash pulmonary oedema is typically sudden in onset, with signs and symptoms of acute pulmonary oedema, and acute systemic hypertension. Stable haemodynamics and respiratory function often return within hours without specific treatment. There is usually a degree of renal impairment and a history of hypertension. A haemodynamically significant unilateral stenosis increases renin secretion from the juxtaglomerular apparatus, causing sodium and water retention by the contralateral kidney. A normal contralateral kidney suppresses its renin secretion and a renovascular stenosis, requiring intravascular volume. If there is bilateral renal artery stenosis, or an abnormal contralateral kidney this does not happen and volume overloading can occur. Renal artery stenosis can be treated by PTCA or surgical revascularisation.