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

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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, 1997, to June, 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 20-point score), duration of rotavirus shedding, and seroresponse to rotavirus were compared between HIV-infected and HIV-uninfected children.

Findings 786 inpatients (median age 8 months, 271 [34%] of whom were HIV-1-infected) and 400 outpatients (median age 9 months, 65 [16%] of whom were HIV-infected) were enrolled. Rotavirus was detected less frequently among HIV-infected children (102 of 336 [30%]) than among HIV-uninfected children (348 of 850 [41%]), (relative risk 0·71 [95% CI 0·53–0·87], p=0·0007). There were no differences in rotavirus disease severity for hospitalised children with and without HIV infection, but HIV-infected children were more likely to die during follow-up (11/50 [22%]) than HIV-uninfected children (0/61, p<0·0001). Of 29 HIV-infected and 45 HIV-uninfected children who completed follow-up, six (21%) HIV-infected children shed rotavirus, compared with two (4%) HIV-uninfected children (4·66 [1·01–21·51], p=0·05), but shedding was not associated with diarrhoea. Three-quarters of children exhibited a four-fold rise of serum IgG or IgA to rotavirus, which did not vary by HIV status.

Interpretation Malawian children with concomitant HIV infection resolved acute rotavirus infections. Rotavirus vaccine safety and immunogenicity in HIV-infected infants should now be determined.

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Introduction

Rotaviruses are the main cause of severe, dehydrating diarrhoea in infants and young children throughout the world.[1] By contrast with more-developed countries, in which rotavirus causes few deaths (<40 per year in the USA),[2] an estimated 500 000 to 870 000 deaths annually are caused by rotavirus infection in less-developed countries.[3,4] Consequently, the development, testing, and introduction of rotavirus vaccines is a public-health priority.[5] Early rotavirus vaccines seemed to be less effective in tropical settings, but newer vaccines have shown similar levels of protection (80–100%) against the most severe outcomes of rotavirus infection in more-developed and less-developed countries.[6,7]

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.[8,9] Although co-infections with rotavirus and HIV have been identified in HIV-endemic areas,[10] 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 immunodeficiency syndromes) can result in severe, protracted, life-threatening diarrhoea, with faecal virus excretion persisting for many months,[11] and extraintestinal rotavirus infections have been reported in immunodeficient children.[12]

Most rotavirus vaccines in development include live, oral, attenuated strains,[1] and concern exists 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),[13] tetravalent rhesus-human reassortant 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.[14] Understanding the behaviour of natural rotavirus infections 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.[15] 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. Blantyre 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-vitro model for assessment of drug susceptibility needs to be developed. Third, 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 that includes a more comprehensive genotypic characterisation of *P carinii* is needed to further elucidate the association between mutations and clinical outcome.

Our results suggest that patients infected with mutant *P carinii* can be successfully treated with co-trimoxazole. Since presence of *DHPS* mutations in patients with *P carinii* pneumonia does not always correlate with response to different treatments, the possibility (or even presence) of a *DHPS* mutation should be only one of several criteria used in guiding the choice of initial drug treatment of *P carinii* pneumonia in patients with HIV-1.

Contributors

Thomas Navin, Charles Beard, Laurence Huang, Carlos del Rio, Norman Pieniazek, and David Rimland participated in the investigation. Thomas Navin, Charles Beard, Laurence Huang, Norman Pieniazek, Allen Hightower, and David Rimland were members of the protocol development team. Charles Beard directed the DNA sequencing, assisted by Norman Pieniazek, Jane Carter, and Thuy Le. Patient enrolment was done by Laurence Huang (San Francisco), Carlos de Rio (Atlanta), and David Rimland (Atlanta VA Hospital). Sherline Lee managed and analysed the data, and statistical analysis was done by Allen Hightower. Thomas Navin, Charles Beard, Laurence Huang, Allen Hightower, and David Rimland contributed to the manuscript.

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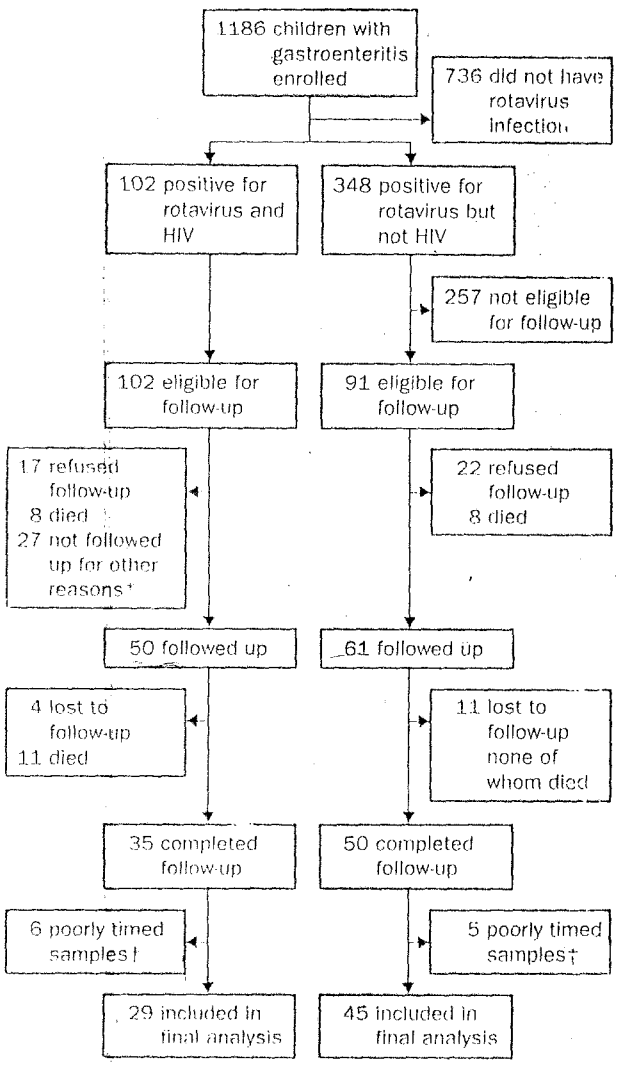

Progress of children who entered follow-up phase of study
*Either because of temporary unavailability of CD4 testing facilities, or because of an equivocal HIV-positive result on initial rapid screen. †Acute serum sample taken >1 week after onset of illness.

negative group (11 of 50 [22%] *vs* 0 of 61, p<0·0001). Death after hospital discharge was often preceded by fever, respiratory symptoms, diarrhoea, 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 (830/μL [39–2273], 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 rates of shedding or seroresponse by age, sex, WAZ score, CD4 count, CD8 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 commonly identified 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 diarrhoea in HIV-infected adults.[22] Although infection with HIV did not result in a younger age of presentation with rotavirus diarrhoea, 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 diarrhoea 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

	HIV positive (n=29)	HIV negative (n=45)	Relative risk (95% CI)	p
Demographics				
Male sex	14 (48%)	28 (62%)	0·71 (0·40–1·25)	0·24
Age (months)*	6 (1–15)	7 (2–22)	..	0·35
Age <6 months	12 (41%)	12 (27%)	1·55 (0·81–2·97)	0·19
CD4 counts				
S1 CD4/μL*	768 (39–2273); n=18	1039 (28–2032); n=30	..	0·61
S1 CD4 <500/μL	6/18 (33%)	8/30 (27%)	1·25 (0·52–3·02)	0·63
S2 CD4/μL*	1038 (133–3096); n=20	1716 (417–5200); n=33	..	0·002
S2 CD4 <500/μL	6/20 (30%)	1/33 (3%)	9·90 (1·28–76·36)	0·005
Shedding by week				
1	2/29 (7%)	1/44 (2%)	3·03 (0·29–30·95)	0·56
2	3/28 (11%)	0/42	..	0·06
3	2/27 (7%)	1/44 (2%)	3·26 (0·31–34·25)	0·55
4	0/29	ND	..	..
Any	6/29 (21%)	2/45 (4%)	4·66 (1·01–21·51)	0·05
Seroresponses (units)				
S2/S1 IgG	8·0	5·0	..	0·37
S2/S1 IgA	3·5	4·5	..	0·43
≥four-fold IgG	13 (45%)	26 (58%)	0·78 (0·48–1·25)	0·28
≥four-fold IgA	22 (76%)	29 (64%)	1·18 (0·87–1·59)	0·30
≥four-fold IgG or IgA	22 (76%)	34 (76%)	1·00 (0·77–1·31)	0·98

S1=acute sample; S2=convalescent sample; ND=not determined. *Median (range).

Table 3: Comparison by HIV status of children who completed follow-up

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 is unclear. In this regard, the effect of natural rotavirus infection on HIV replication remains to be addressed. A higher proportion of HIV-infected than HIV-uninfected children were malnourished in this study, and there is some evidence of greater rotavirus disease severity among malnourished children.[31] However, after controlling for age and HIV status, we found no effect of the WAZ score on the severity of rotavirus diarrhoea.

HIV-infected children were more likely than HIV-negative children to shed rotavirus during follow-up, but in none of these children was this associated with diarrhoea, and the clinical significance of this finding is questionable. Moreover, three-quarters of children showed a four-fold seroresponse to rotavirus after acute infection, and response rates did not differ by HIV status. The host factors necessary for rotavirus clearance in humans are unknown, but in mice, cell-mediated and humoral immune mechanisms have a role in the resolution of rotavirus infection.[24,25] Presumably, at least one of these mechanisms is sufficiently conserved in the small intestinal mucosa of HIV-infected children to enable virus 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 symptomless rotavirus infections of neonates,[1] and a higher prevalence among older children of serotype G9 rotaviruses has been reported from the UK.[26] A possible explanation for the strain-specific age differences seen in this study could be that P[6],G8 strains have only recently been introduced into the human population in Malawi, and a lack of passively acquired neutralising maternal 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 by strain type. Although convincing evidence is lacking that severity of diarrhoeal illness varies by strain, a study from Bangladesh found that rotavirus serotypes G2 and G3 were associated with the most severe dehydration, but this finding did not seem to be of major clinical importance.[27]

The findings of this study, taken together with those of smaller cross-sectional[10] and longitudinal[28,30] 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-up, 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 default, the demographic characteristics of children who were lost to follow-up did not differ from those who completed the study. Finally, since we did not attempt to detect viral RNA by RT-PCR, we have probably underestimated the rate and duration of rotavirus shedding. By RT-PCR, Richardson and colleagues[11] showed that 30% of healthy children admitted to hospital with severe rotavirus diarrhoea excrete virus in stool for more than 20 days after onset of diarrhoea (up to a maximum of 57 days), which might be associated with symptoms of mild diarrhoea.

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 could mount a seroresponse similar to children without HIV infection. The finding of more frequent deaths 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 inapparent) prolonged shedding in some HIV-infected children also merits further investigation, and would be best addressed in a large, longitudinal study with long-term follow-up. Finally, this work should now encourage careful studies of the safety and immunogenicity of rotavirus vaccines in HIV-infected infants. The possible effect of rotavirus vaccine on host HIV disease needs assessment, and the possibility of prolonged excretion of vaccine virus should be considered. Such studies would represent a significant advance towards the goal of reducing childhood mortality from rotavirus across Africa, through the routine rotavirus vaccination of infants.[32,33]

Contributors

Nigel Cunliffe, Jailosi Gondwe, Stephen Graham, Robin Broadhead, Malcolm Molyneux, and C Anthony Hart were responsible for study design; Nigel Cunliffe, Jailosi Gondwe, Stephen Graham, and Ndina Nhlane supervised the collection of clinical data and samples; Carl Kirkwood did the rotavirus IgG and IgA assays; Nigel Cunliffe, Benson Thindwa, and Winifred Dove carried out the rotavirus and HIV ELISA assays; and Nigel Cunliffe wrote the paper with major contributions from C Anthony Hart and Malcolm Molyneux.

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Uses of error: Ignoring the obvious

Over 40 years ago, as a young registrar, I looked after the third child in a young family. The firstborn had died in the university paediatric hospital in Athens, in July, with a diagnosis of encephalitis at the age of 12 months. The second child had died, in June, at the age of 3 months with pneumonia, in a private paediatric clinic. This two-month-old baby was developing normally, but the parents were understandably anxious about her. When she was 9 months old her father told me that when he ate tinned sardines the child liked to lick the cans. I told him to discourage her from doing this. I didn't hear anything more until I saw her at 14 months of age when she was admitted to the children's hospital in Athens with vomiting and prostration. She was hyponatraemic and hypochloraemic, but her full blood count, thyroid hormones, urinary steroids, and plasma cortisone were all normal. I considered that she had an electrolyte disturbance of unknown cause and prescribed one gram of salt daily during the summer months.

The following summer, she started vomiting and collapsed again. She was admitted to hospital and when we finished inserting an intravenous drip, the nurse kissed the child to calm her. She told me that the child's sweat was salty. A sweat test was abnormally high in chlorine (130 meq/L). The child transferred to the cystic fibrosis clinic, and appropriate treatment and family counselling started. I had ignored three important facts: one, all three siblings became ill during the summer, two, the infant suffered from salt insufficiency (she licked sardine cans), and three, serum chlorine and calcium were low. These errors are an important reminder that cystic fibrosis may present in hot climates as heat exhaustion.

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Case report

Flash pulmonary oedema

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A 68-year-old man was admitted with back pain and vomiting. He had a history of angina, hypertension, right renal artery stenosis, and an elective abdominal aortic aneurysm repair in 1997. 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 8 mm Hg. At the time of his infarct his renal function was impaired, but comparable to that recorded in 1997 (urea 18 mmol/L, creatinine 187 µmol/L). His renal function deteriorated transiently following angiography (urea 32 mmol/L, creatinine 546 µmol/L) but improved after 48 hours of intravenous fluids (urea 25 mmol/L, creatinine 426 µmol/L). He was then discharged and outpatient follow-up was arranged. On this admission he was unwell and oliguric. His renal function had deteriorated substantially with a urea of 36 mmol/L, and creatinine of 958 µmol/L. He was taking furosemide 40 mg daily, aspirin 75 mg daily, diltiazem 180 mg twice daily, isosorbide mononitrate 50 mg daily, ramipril 5 mg daily, and calcium polystyrene sulfonate. He was transferred to intensive care for haemofiltration and diltiazem and ramipril were discontinued. Soon after transfer he became hypoxic and was intubated and ventilated. He had widespread expiratory wheezes on auscultation and chest radiograph showed bilateral interstitial shadowing. He improved rapidly and was extubated within 24 h, but only 12 h later he was re-intubated following another acute desaturation. Two further episodes occurred, each resolving spontaneously and on the fourth re-intubation, a pulmonary artery catheter was inserted. His pulse rate was 100 bpm, systemic arterial pressure 190/110 mm Hg, venous pressure 10 mm Hg, pulmonary artery pressure 70/40 mm Hg, and pulmonary capillary wedge pressure 35 mm Hg. No new abnormalities were detected on electrocardiography and transthoracic echocardiography.

As the patient had good left ventricular function, we considered a renovascular aetiology for his episodes of pulmonary oedema. Renal arteriography showed a severe right renal artery stenosis with a trans-stenotic gradient of 10 mm Hg (figure). Percutaneous balloon angioplasty (PTCA) was done, with a good angiographic result, eliminating the trans-stenotic pressure gradient. He remained stable for the next 48 h with no further episodes of acute pulmonary oedema and was then transferred to the regional renal unit for haemodialysis.

Renal artery stenosis is a rare cause of acute pulmonary oedema. So-called "flash" pulmonary oedema can indicate

Renal arteriograph showing right renal artery stenosis

the presence of unilateral or bilateral obstructive renal arteriosclerosis.[1] Most patients have co-morbid cardiovascular disease and a renovascular aetiology is overlooked.[2] 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.[3] A haemodynamically-significant unilateral stenosis increases renin secretion from the juxtaglomerular apparatus, causing sodium and water retention by the ipsilateral kidney. A normal contralateral kidney suppresses its renin secretion and a natriuresis occurs, restoring intravascular volume. If there is bilateral renal artery stenosis, or an abnormal contralateral kidney this does not happen and volume overloading can occur.[4] Renal artery stenosis can be treated by PTCA or surgical revascularisation.[5]

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