A year's experience of the rotavirus syndrome and its association with respiratory illness

HELEN M. LEWIS, J. V. PARRY, HEATHER A. DAVIES, RUTH P. PARRY, ANGELA MOTT, R. R. DOORMASHKIN, P. J. SANDERSON, D. A. J. TYRRELL, AND H. B. VALMAN

Department of Paediatrics, Division of Communicable Diseases, Section of Electron Microscopy, Department of Microbiology, and Division of Medical Computing of Northwick Park Hospital, and Clinical Research Centre, Harrow

SUMMARY In a hospital study rotavirus was identified in 51% of 152 children with diarrhoea. These patients showed a clinical pattern that was distinct from patients in whom the diarrhoea was associated with bacteria, other viruses, or no pathogens. A respiratory illness was described in 66% of rotavirus patients and usually preceded the gastrointestinal symptoms. Vomiting lasted between one and 3 days and was curtailed by substituting the normal diet with clear fluids. Watery diarrhoea continued for 4 or 5 days, even when rehydration was by the intravenous rather than the oral route. Prolonged diarrhoea was rare. Most children infected with rotavirus were under 2 years of age, but dehydration was most severe in infants aged between 12 and 18 months. A clinician can thus recognise the rotavirus syndrome and expect spontaneous recovery if adequate rehydration is maintained for a critical few days.

The clinical features of patients admitted to hospital with gastroenteritis were studied in north-west London between 1968 and 1970 (Sinha and Tyrrell, 1973). The results showed that there was a distinct nonbacterial, winter epidemic disease which mainly affected children under 2 years and was often associated with symptoms and signs in the respiratory tract. An 'infantile gastroenteritis virus' was predicted and this was soon proved correct. Reports have universally shown that rotavirus particles can be seen in the stools of 15 to 90% of infants with diarrhoea but are absent from the stools of most healthy children. The highest isolation rates have been in temperate climates, particularly in the winter months (Bishop *et al.*, 1974; Davidson *et al.*, 1975; Kapikian *et al.*, 1976; Dupont *et al.*, 1977; Konno *et al.*, 1977; Schoub *et al.*, 1977; Walker-Smith, 1978).

Northwick Park Hospital and Clinical Research Centre, Harrow

HELEN M. LEWIS, senior paediatric registrar
HEATHER A. DAVIES, research officer
RUTH P. PARRY, medical laboratory scientific officer
ANGELA MOTT, statistician
R. R. DOORMASHKIN, head of section of electron microscopy
P. J. SANDERSON, consultant microbiologist
D. A. J. TYRRELL, head of division of communicable diseases
H. B. VALMAN, consultant paediatrician
Central Public Health Laboratory, London
JOHN V. PARRY, senior medical laboratory scientific officer

Most observations of the clinical features of rotavirus infection indicate that vomiting is common (Shepherd *et al.*, 1975; Rodriguez *et al.*, 1977; Tallet *et al.*, 1977) and dehydration can be severe (Rodriguez *et al.*, 1977; Tallet *et al.*, 1977). Concurrent respiratory symptoms have been noted in retrospective analysis but have not proved significantly more frequent than in cases where diarrhoea is not associated with rotavirus (Carr *et al.*, 1976; *British Medical Journal*, 1977a; Rodriguez *et al.*, 1977; Tallet *et al.*, 1977). Because of possible omission of relatively mild respiratory symptoms in a predominantly gastrointestinal illness these studies do not show the true incidence or importance of respiratory tract involvement.

The patients in this prospective study lived in the same geographical area as those reported in 1968-70 (Sinha and Tyrrell, 1973). The aims were to define the clinical features of rotavirus infection and to explore the association between respiratory illness and pathogen in infantile gastroenteritis.

Patients and methods

The patients were children admitted to the paediatric or infectious diseases unit of Northwick Park Hospital during a complete year (1977); they had

passed frequent loose stools for at least 24 hours at some stage of their illness and required replacement of the normal diet with clear fluids. Nearly all children were examined by the same clinician within 24 hours of admission and each day thereafter, and the findings were recorded on a standard form. Stools and throat swabs were collected once from each child as early in the illness as possible. Stools were studied by electron microscopical examination for rotavirus. The stools and throat swabs were cultured for viruses and for pathogenic bacteria. From some children who had signs of respiratory illness, nasopharyngeal secretions were aspirated and material from a plain throat swab was smeared on to a glass slide. These were stored, and 10 specimens were later examined by electron microscopy because virus particles were seen in the corresponding faecal specimens.

Stools for virology were sent immediately to the laboratory or stored at -70°C . A 10% suspension of stool was prepared in nutrient broth containing penicillin, streptomycin, and amphotericin B. The suspension was centrifuged at 2500 *g* for 10 minutes, then the supernatant was centrifuged at 10 000 *g* for 30 minutes at 4°C to remove bacteria. This supernatant was used for electron microscopical examination and for virus isolation tests. For electron microscopy 2 ml of faecal extracts were ultracentrifuged at 100 000 *g* for one hour at 4°C , and the deposit was negatively stained with potassium phosphotungstate using a technique described elsewhere (Flewett *et al.*, 1974). Grids were examined in a Philips EM 300 at a viewing magnification of 28 000.

For viral culture, 0.2 ml of stool suspension was inoculated into 2 tubes of each of 3 types of tissue cultures: human embryonic lung fibroblasts (MRC 5), Ohio HeLa cells, and secondary monkey kidney cells. Inoculated tissue cultures and uninoculated controls were incubated in roller drums at 33°C .

Throat swabs for virus isolation were taken on sterile plain cotton swabs and broken into virus transport medium (nutrient broth with antibiotics). If possible, throat swabs were kept at 4°C until inoculation. Within 2 hours 0.2 ml of the fluid was inoculated into 2 tubes of each of the 3 tissue cultures.

Viruses from both stools and throat swabs were detected by their cytopathic effects. Haemadsorption tests were performed on monkey kidney cells which were inoculated with respiratory specimens. Some adenovirus and enterovirus isolates have not been serotyped. Cultures were incubated for 4 weeks before they were discarded as negative.

Nasopharyngeal secretions were aspirated after injection of 2 ml normal saline into each nostril. This material was ultracentrifuged at 100 000 *g*

for one hour. The resulting pellets were fixed in glutaraldehyde and osmium tetroxide buffered solutions, embedded in Spurr resin and sectioned. Sections were stained with uranyl acetate and lead, and examined for virus particles by electron microscopy. Both the nasopharyngeal secretions and the smeared slides from throat swabs were examined by negative staining (Flewett *et al.*, 1974).

For bacteriology fresh stool specimens were plated on to deoxycholate agar and MacConkey's medium, and inoculated into selenite broth. Enteropathogenic *Escherichia coli* were identified using antisera (Central Public Health Laboratory, Colindale) to 15 recognised enteropathogenic types. From April 1977 a selective medium was used to isolate campylobacter species (Skirrow, 1977). Microscopical examination of stool specimens for parasites was performed if there had been diarrhoea for more than 10 days or if the child had recently returned from abroad.

Bacterial throat swabs were taken on sterile serum-coated wool buds and transported in Stewart's medium. They were cultured on blood and chocolate agar. Colonies were identified by standard techniques and all streptococci were grouped serologically.

The completed clinical and microbiological data were punched on to computer cards. Tables and significance tests were produced by computer analysis (Nelder, 1974).

Results

A total of 150 children were studied and 8 were rejected because they did not pass any stools after admission. Two children were admitted twice, but as both were asymptomatic between admissions each illness was considered as a separate episode. Thus 152 episodes of diarrhoea were investigated and these were divided into 5 groups according to the pathogens identified in the faeces (Table 1).

The largest was group 1 containing 74 patients from whom rotavirus was detected, although on tissue culture, 6 of these also showed an adenovirus and 3 an enterovirus.

Table 1 Results of testing faeces

Group	Stool pathogens	Patients <i>n</i> = 152	
		No.	(%)
1	Rotavirus	74	(49)
2	Pathogenic bacteria	23	(15)
3	Other viruses	26	(17)
4	No pathogens	26	(17)
5	Rotavirus and pathogenic bacteria	3	(2)

Group 2 contained 23 patients with pathogenic bacteria: salmonella 9, shigella 8, enteropathogenic *E. coli* 1, and campylobacter species 5. Of these, one child had *Giardia* on light microscopy and 2 showed an adenovirus, detected by tissue culture.

Group 3 contained 26 patients from whom viruses other than rotavirus were the only pathogens identified. The results of tissue culture were: adenovirus 9, enterovirus 9. Electron microscopical examination showed adenovirus 3, enterovirus 3, astrovirus 1, coronavirus 1, and calicivirus 2. On only 2 occasions was a virus of the same type (both adenoviruses) found by tissue culture as well as by electron microscopy.

In the stools of patients in group 4 no pathogens were found. Group 5 contained 3 patients who showed both rotavirus and pathogenic bacteria—*Salmonella berkeley*, *Salmonella typhimurium*, and *E. coli* O125.

Altogether 125 throat swabs were taken for virology and results of 17 (14%) were positive; they yielded adenovirus 4, enterovirus 2, cytomegalovirus 5, herpes simplex 1, respiratory syncytial virus 1, rhinovirus 3, and parainfluenza 1. 135 throat swabs were taken for bacteriology and results of 22 (16%) were positive; they comprised streptococci group A 3, streptococci group B 5, streptococci group C 1, *Streptococcus pneumoniae* 4, *S. faecalis* 1, and haemophilus species 8. In 5 patients a virus of the same group was isolated from both stool and throat (adenovirus 4, and enterovirus 1). The throat swabs and nasopharyngeal secretions examined by electron microscopy belonged to 9 patients with rotavirus and one with an adenovirus seen on stool electron microscopy. A papilloma virus was found in material from the throat swab of one patient who had rotavirus in the stool but no virus particles were identified in any other respiratory specimen.

The clinical features of the 4 main groups of stools were compared but the 3 patients in group 5 were excluded. The results for all 4 groups were tested for nonuniformity by the χ^2 test and reported as significant when $P < 0.05$. Clinical features were recorded before any microbiological results were received. Bacteriological reports were obtained within 3 days, but virology and electron microscopical examination were not completed until after the patient had been discharged from hospital and so could not bias the clinical observations.

At least one dose of an antibiotic was known to have been taken by 46 children before admission. These children included a few with bacterial infections, but the differences between the groups were not significant (35.5%, 17%, 27%, and 35% respectively, for groups 1 to 4).

Patients.

Sex

There were 88 (59%) boys and 62 (41%) girls. Sex ratios in the 4 stool groups were 58%, 65%, 58%, and 62% boys in groups 1 to 4 respectively, and these were not significantly different.

Age

Fig. 1 shows the ages of the patients. The youngest was 8 days old and the oldest 13 years. The 4 groups showed different patterns ($\chi^2 = 42.9$, $P = 0.008$). Rotavirus was most common in babies of between 6 and 18 months, and other viruses or no pathogens below 6 months, but bacterial pathogens occurred in fairly equal numbers at each age. 15 (10%) patients were less than 3 months of age and rotavirus was identified from only 2 of these babies.

Month of admission

Fig. 2 shows the seasonal pattern of admissions. Rotavirus infection occurred mainly in the first 6 months of the year with a peak in January and February. The other groups showed no pronounced seasonal pattern.

Fig. 1 Age distribution of the patients.

Fig. 2 Monthly incidence of gastroenteritis.

Clinical features.

Vomiting

69 (93%) out of 74 patients excreting rotavirus vomited for at least one day, compared with 10 (43%)

out of 23, 14 (54%) out of 26, and 20 (77%) out of 26 in groups 2 to 4 respectively ($\chi^2 = 32.6$, $P < 0.001$). Fig. 3 shows the number of patients who vomited for at least one, for at least 2, etc. days before and after admission, but not necessarily on consecutive days. In group 1 the median duration of vomiting was one to 2 days before admission, after which most patients either did not vomit at all or had stopped within 24 hours. A similar pattern was observed in the other groups. In groups 3 and 4 proportionately fewer patients vomited but they tended to vomit for longer ($\chi^2 = 42.60$, $P = 0.009$).

Diarrhoea

Patients were only included in the study if they had diarrhoea for at least one day, and Fig. 4 shows the number of days on which this was reported before and after admission. In the rotavirus group diarrhoea usually persisted for 2 to 3 days after admission, and the median total duration of diarrhoea was 4 to 5 days, with a mean of 5. In the other groups it lasted significantly longer, means of 7.3, 9.1, and 8.5 days in groups 2 to 4 respectively ($\chi^2 = 51.5$, $P = 0.003$). Blood in the stools was recorded only in the group with bacterial infection (10 (38%) out of 26) and in one patient in whom no pathogens were found.

Severity of dehydration

Intravenous fluids were administered to children with more than 5% dehydration clinically, and also to those who continued to vomit after they were given oral glucose electrolyte mixture. The use of IV fluids was taken as an index of the severity of dehydration. More rotavirus patients had IV fluids (39%), compared with 13%, 12%, and 23% in groups 2 to 4 respectively ($\chi^2 = 11$, $P = 0.01$).

Fig. 3 Number of days on which vomiting was recorded.

Fig. 4 Number of days on which diarrhoea was recorded.

Fig. 5 shows the proportion of patients of various ages that received IV fluids in the rotavirus group compared with the others. In the rotavirus group there was a highly significant peak at 12 to 18 months, when 75% of patients excreting rotavirus were given IV fluids and 3 of them had hypernatraemic dehydration (plasma sodium >155 mmol/l).

Fig. 5 Relationship between age and treatment with intravenous fluids.

Respiratory infection

Observations showing that the respiratory tract was affected are summarised in Table 2. A patient was classified as having respiratory involvement from all evidence of respiratory illness, either by the history or by clinical observations; on this basis 66% of rotavirus patients had respiratory illness compared with 26 to 38% of other groups ($\chi^2 = 16$, $P = 0.01$).

There was no correlation between a positive bacterial or viral throat swab and respiratory illness ($\chi^2 = 0.07$, $P = 0.03$), nor with the patient being in the rotavirus or any other group ($\chi^2 = 4.1$, $P = 0.25$).

Incidence of fever

62% of rotavirus patients had a maximum recorded rectal temperature of 37.5°C or more compared with 57%, 58%, and 58% in the other groups, but the differences were not significant ($P = 0.05$).

Discussion.

This study shows that diarrhoea attributed to rotavirus is more often associated with a respiratory illness than is diarrhoea attributed to other pathogens. A history of a preceding cough, nasal discharge, or otitis media was the outstanding clinical difference between rotavirus patients and the others. Likewise, after admission to hospital a red throat or red, bulging tympanic membranes were seen more often in the rotavirus patients than in others. Viruses and bacteria were isolated with equal frequency from the throat swabs of patients with respiratory symptoms as from those with no such symptoms. This suggests that the rotavirus, rather than any

Table 2 Evidence of respiratory infection

Clinical features	Group 1 (rotavirus)	Group 2 (bacteria)	Group 3 (other viruses)	Group 4 (no pathogens)	Significance
*History of cough, nasal discharge, or otitis before admission	40/74 (54)	3/23 (13)	7/26 (27)	7/26 (27)	$\chi^2 = 13.4$ $P = 0.04$
*Red throat observed in hospital	30/74 (41)	4/23 (17)	5/26 (19)	3/26 (12)	$\chi^2 = 11.5$ $P = 0.009$
Fluorid otitis media	20/74 (27)	3/23 (13)	2/26 (8)	3/26 (12)	$\chi^2 = 6.78$ $P = 0.08$
Nasal discharge	17/74 (23)	4/23 (17)	7/26 (27)	4/26 (15)	$\chi^2 = 1.36$ $P = 0.7$
Persistent cough	8/74 (11)	1/23 (4)	4/26 (15)	2/26 (8)	$\chi^2 = 1.85$ $P = 0.6$
Hoarse voice	3/74 (4)	0	2/26 (8)	0	$\chi^2 = 3.32$ $P = 0.34$
Lower respiratory tract infection	5/74 (7)	0	3/26 (12)	1/26 (4)	$\chi^2 = 3.15$ $P = 0.37$
*Any evidence of respiratory infection	49/74 (66)	6/23 (26)	8/26 (31)	10/26 (38)	$\chi^2 = 16.1$ $P = 0.01$

*Features occurring significantly more often in rotavirus patients ($P < 0.05$). Percentages are shown in parentheses.

other agent, was responsible for the respiratory features.

However, no rotavirus particles were found by electron microscopical examination of nasopharyngeal secretions and throat swabs from 9 children with rotavirus in their stools and signs of an upper respiratory infection. The rotavirus may have been present in the upper respiratory tract at an earlier stage in the illness or in concentrations too low to be detected by electron microscopy (Davidson *et al.*, 1975).

Although this study showed a seasonal peak in winter (Fig. 2), rotavirus was isolated throughout the year. In temperate climates there may be endemic infection with superimposed winter epidemics; in tropical countries rotavirus is isolated particularly in the rainy season and is more common in areas of high humidity (T. H. Flewett, 1978, unpublished observation). Epidemics could be related to different serotypes (Fonteyne *et al.*, 1978; Zisis and Lambert, 1978) and transmitted by droplet infection via the respiratory tract, while endemic infection may be transmitted by the faeco-oral route.

Rotavirus illness was usually accompanied by vomiting which preceded the diarrhoea (Fig. 3). After admission to hospital, vomiting stopped but diarrhoea persisted for 2 or 3 days (Fig. 4). A few patients became rapidly dehydrated as a result of passing profuse watery stools even when they were receiving IV fluids only. The observation that diarrhoea attributed to rotavirus lasted for up to 5 days, despite admission to hospital, suggests that rational treatment can be planned from a clinical recognition of the syndrome. In the past, schemes for the management of dehydration associated with gastroenteritis have been constructed mainly for infants under one year of age infected with enteropathogenic *E. coli*. An electrolyte mixture is customarily given

orally or intravenously for 24 hours; then the child is gradually weaned to full strength milk over 5 days. For the rotavirus syndrome it may be preferable to give an electrolyte mixture for 2 or 3 days, and then regrade rapidly if dilute milk or a light diet is tolerated. Our children were usually on a normal diet after 5 days and this regimen rarely produced prolonged diarrhoea.

The most severely dehydrated children excreting rotavirus were aged between 12 and 18 months, only 2% of the whole series had hypernatraemic dehydration and there was only one patient with persistent disaccharide intolerance. Recent surveys from Hackney (London) and Newcastle upon Tyne show a decline in the duration and severity of infantile gastroenteritis (British Medical Journal, 1977b; Pullan *et al.*, 1977; Tripp *et al.*, 1977) but severe dehydration and prolonged diarrhoea were still common in the very young babies. In the present study only 10% of the children were under 3 months, and from the younger babies other viruses or no pathogens were found in the stools more often than rotavirus. A comparatively high incidence of early breast feeding in the area served by this hospital (Coles *et al.*, 1978) may account for the rarity of both recognised enteropathogenic serotypes of *E. coli* and early infection with rotavirus (Bullen, 1977; Thouless *et al.*, 1977). The practice of feeding low solute milks for the first months of life may have helped to prevent severe dehydration and hypernatraemia.

Comparison between this study and others in the UK should take into consideration the social and cultural background of the indigenous population. Neither social class nor ethnic group was recorded on the proforma, but in retrospect, 66 (44% of the total) patients were children of immigrants to this country who were predominantly Asian refugees

from East Africa. Many lived in over-crowded accommodation and, in some cases, bacterial infection was imported from overseas either by the child himself or by another member of the household.

Rotavirus (group 1) and bacterial (group 2) patients should be compared with caution with groups 3 and 4 in which the nature of the pathogen is not established. No pathogens were found in 17% of children but there may have been unidentified viruses, or enteropathogenic strains of *E. coli* which were not detected by the serological methods used. Other studies show that complement-fixation tests on paired sera can detect rotavirus in patients whose stools were negative by electron microscopical examination (Kapikian *et al.*, 1975; Gomez-Barreto *et al.*, 1976; Gust *et al.*, 1977); as such examination is usually negative by 6 days after the onset of diarrhoea, rotavirus may have been missed in 8 cases with a longer history.

Except in the neonatal period, rotavirus is rarely identified in the stools of asymptomatic children (Albrecht and Murphy, 1976; Totterdell *et al.*, 1976; Gust *et al.*, 1977; Murphy *et al.*, 1977) but the same is not true of other stool viruses (Stott *et al.*, 1967; Flewett *et al.*, 1974; Flewett, 1976; Madeley *et al.*, 1977). This study did not include a group with no diarrhoea but it was conducted concurrently with a study of viruses isolated from children of the same age who were admitted with febrile convulsions (Lewis *et al.*, 1979). There was no significant difference in the rate of isolation of enteroviruses or adenoviruses from the stools of these two groups of patients, but rotavirus was found in only 2 (3%) out of 62 children with febrile convulsions and each had a febrile illness followed by diarrhoea. Two children in the gastroenteritis study had febrile convulsions. One had an adenovirus isolated from the throat and stool and the other was infected with *Shigella sonnei*.

Despite the limitations of the comparative analysis, this survey has shown distinctive clinical features in patients excreting rotavirus; in particular, diarrhoea was not usually the first symptom. General practitioners and paediatricians should therefore consider rotavirus in the differential diagnosis of vomiting, unexplained dehydration, pharyngitis, acute otitis media, or an unexplained fever, particularly in children from 6 to 24 months of age and in winter.

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Correspondence to Dr Helen Lewis, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ.

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