the latter two have some use in the treatment of herpes infections. Vidarabine has been successfully used intravenously and topically for herpes encephalitis and ocular infections, respectively, provided therapy is initiated early in the course of illness. Recently concluded randomized placebo-controlled clinical trials with topical acyclovir demonstrated that the drug does alleviate symptoms and hastens healing of the lesions of first infections. To date, however, it has not been shown to be effective for recurrent infections or that recurrences are prevented.

In summary, available data indicate that an epidemic of herpes simplex type 2 infections is currently taking place in the United States. The lack of a specific cure and methods to control its spread preclude any attempts to interrupt transmission and control the epidemic. Furthermore, the limited available information does not estimate the personal costs in terms of human suffering or the economic costs incurred by desperate patients searching for a cure for their repeated infections.


Rotaviruses

Introduction

Acute diarrheal diseases have long been recognized as a major public health problem throughout the world. Recent technological advances during the past decade, however, have now permitted the identification of viruses in feces during the acute stage of disease. This breakthrough has enabled scientists to assign a viral etiology to many diarrheal episodes in infants, young children, and adults in developed and developing countries.

Rotaviruses have emerged as the single most important worldwide cause of diarrhea in infants and young children requiring admission to hospitals for the treatment of gastroenteritis. Infection with these viruses also accounts, to some extent, for malabsorption and malnutrition in infants, especially in developing countries. Identification, characterization, and a clearer understanding of rotavirus diarrheas is necessary in order to find measures to prevent their transmission and, most importantly, to develop suitable vaccines and appropriate technologies which can be effectively adapted to the needs of all countries.

This article is the first of a two-part series which reviews new knowledge and understanding of many aspects of rotavirus diarrheas. Part I deals with the clinical features and epidemiology of rotavirus. Part II will present laboratory methods for the detection and identification of rotaviruses.

The Virus

In 1973 rotavirus was first detected in a human reservoir in Melbourne, Australia, by thin-section electron microscopic examination of duodenal biopsies obtained from children with acute diarrhea. Shortly afterwards, in Australia, Canada, the United Kingdom, and the United States, it was detected by electron microscopic examination of diarrheal stool specimens. The virus is 70 nM in size, contains RNA, and has an inner and outer capsid. The name is derived from the Latin word “rota,” meaning wheel, which it resembles in appearance. It has also been referred to as “orbivirus,” “duovirus,” “reovirus-like agent,” and “infant gastroenteritis virus.”

Clinical Features of Rotavirus

The incubation period of rotavirus enteritis ranges from one to seven days, and is usually less than 48 hours. Excretion of rotavirus frequently precedes the onset of symptoms; however, in severe infection this has been observed more frequently in males than in females, as is the case with many other diseases in the early years of life.

The symptoms of enteritis vary according to the age of the patient and present similar characteristics to those seen in infections with other enteric pathogens. In newborn babies, diarrhea may be minimal with mild transient temperature elevation. In this case, treatment is usually not required, although infected babies may be slow to regain their birth weight. In infants and young children, the onset of disease is usually marked by explosive and watery diarrheas, often accompanied by mucus which is found in the stool in approximately 25 per cent of cases. Vomiting is often a prominent early symptom and may precede diarrhea. In addition, mild temperature elevation occurs
in about 30 to 50 per cent of patients. Concurrent respiratory symptoms, pharyngitis, and otitis media have also been observed, but whether rotavirus per se is directly responsible for causing these clinical descriptions is not known; to date, rotavirus particles have not been demonstrated in situ in such instances.

The average duration of illness due to rotavirus infection is approximately 5 to 7 days. Virus shedding in the stool commonly continues for up to 10 days and has been observed for as long as 29 days. In immunodeficient children, rotavirus infections can persist for months.

In older children and adults, the symptoms are similar, although usually less severe. Vomiting is less frequent and associated respiratory symptoms have rarely been described. In this age group, diarrhea is usually not life-threatening, although death occasionally occurs in elderly patients.

In childhood diarrhea, dehydration and electrolyte imbalance can often be fatal if not properly treated. Treatment consists of administering oral rehydration solution to all but the most severely dehydrated cases, i.e., patients who are unable to drink, or patients with intractable vomiting. In many developing countries, the glucose-electrolyte oral rehydration salt (ORS) solution, developed originally for the treatment of cholera, has been used repeatedly with successful results for rehydrating patients with rotavirus diarrhea.

Studies of the pathophysiology of rotavirus diarrhea have revealed a sequence of events in the small intestine consisting of infection of the absorptive villous epithelial cells, replacement of the tall columnar villous epithelial cells with cuboid cells, shortening of the villi, lymphocytic infiltration of the villous lamina propria and repair. Such changes appeared in a cephalocaudal direction and suggest that diarrhea may be related to a loss of absorptive capacity in the small intestine. In addition to their loss of absorptive surface area, the villi are covered by undifferentiated crypt cells that lack the ability to digest disaccharides in the diet. Although the exact importance of rotavirus as a contributing factor to malnutrition is not known, the resulting malabsorption of fats and secondary sugar intolerance could theoretically initiate or exacerbate malnutrition. Similarly, there is little documentation on morbidity and mortality due to rotavirus infections in children already suffering from malnutrition.

Epidemiology

Rotavirus enteritis is a disease which appears to have a worldwide distribution generally affecting infants and young children. It is the most frequently observed virus in stools of those in this age group, with diarrhea in almost all investigated areas in the world. The majority of cases are children 6 to 24 months old representing a peak incidence at 9 to 12 months. In a number of hospital-based studies carried out in infants and young children in developed and developing countries, rotavirus has been detected in approximately 50 per cent of diarrhea cases, sometimes with seasonal variation. In other studies, the number of male cases is 20 per cent higher than that of female cases, however, it is not known whether this is due to a greater susceptibility or exposure of male children, or to a higher likelihood of their being brought for medical care. Data from community-based studies are much more limited. Studies carried out in Guatemala and Bangladesh suggest that rotavirus accounts for approximately 10 to 20 per cent of all community diarrhea cases.

Numerous studies on the monthly and annual frequency of rotavirus infection in children admitted to hospitals with acute diarrhea have been undertaken in both tropical and temperate countries. Incidence rates vary with techniques used for detection, but, in general, rotavirus infection accounts for 20 to 40 per cent of diarrheas in children up to five years of age admitted to hospitals in tropical countries, and 40 to 60 per cent of such cases in temperate countries.

In contrast, there are few studies in either developing or developed countries that document the true incidence rate of rotavirus infection. One study in Washington, D.C., USA, found that 3.7 per 1,000 children in the community aged less than 12 months, 2.2 per 1,000 aged 13 to 24 months, and 0.18 per 1,000 aged 25 to 60 months were hospitalized each year with rotavirus infection. A community-based study in rural Bangladesh, associated rotavirus with 4.7 per cent of all diarrheal episodes in children aged two to 60 months (but 39 per cent of all episodes associated with dehydration); incidence rates were 0.5 episodes of rotavirus diarrhea per child per year during the first two years of life, decreasing to a negligible level thereafter. Additional community-based studies in Guatemala and rural El Salvador showed that between 7 and 14 per cent of all diarrheal episodes in children under three years of age were due to rotavirus and that almost all children could expect to have at least one episode of rotavirus diarrhea during their first three years of life.

Mortality rates from rotavirus diarrhea are low in developed countries and virtually unknown in developing countries. Of interest are observations made in Bangladesh, Ethiopia, Finland, and Guatemala which indicate that rotavirus diarrhea is more likely to bring children below the age of two years to treatment facilities than any other diarrheal infection. This suggests that the disease is more likely to result in death if left untreated.

Recent evidence has also demonstrated the existence of more than one serotype of human rotavirus. Workers in Belgium, using a complement-fixation assay and immune electron microscopy, in England, using neutralization of immunofluorescent foci, and in the USA, using an enzyme-linked immunosorbent assay (ELISA), have all defined two distinct serotypes. These serotypes appear to be widely distributed geographically. In the Washing-
ton, D.C. metropolitan area, the sera of most children aged two years contained antibodies to both serotypes, and in hospitalized patients type 2 rotavirus was seen more frequently. In addition, studies of patients who experienced sequential infections revealed that illness caused by one serotype did not provide protection against illness caused by the other serotype. It is not certain whether other serotypes exist; however, workers in England using a fluorescent neutralization test have claimed to have found two other serotypes.

**Seasonality**

It has been clearly demonstrated in studies performed in North America, England, and Australia that rotavirus disease is more prevalent during the colder seasons of the year. One exception may be infection in newborns, in Sydney, Australia, where no seasonal variation was found when rotavirus infection was studied in newborn nurseries. Whether this seasonal pattern occurs in developing countries with tropical climates is unclear. In studies from Venezuela and Costa Rica, little or no seasonal variation in occurrence has been observed; however, in studies from Vellore and Kozhi-kode (Calicut), India, and Bangladesh, rotaviruses have been found most frequently in stool samples collected from diarrhea cases between November and March, the coolest months of the year. In the Vellore study, as in the Australian study cited above, rotaviruses were present in the neonatal nursery throughout the year. One small study conducted in Mexico City, where almost no seasonal difference in temperature occurs, revealed a peak of cases in the autumn months.

**Transmission**

All evidence to date indicates that rotavirus infection spreads by fecal-oral transmission; this has been confirmed by volunteer and animal experiments. There is no evidence, however, which suggests that rotavirus multiplies with production of infectious particles other than in small bowel enterocytes.

Although immunoglobulin A (IgA) specific antibody has been found in the colostrum and breast milk of lactating mothers in a number of countries, it is not clear what role breast milk plays in protection against rotavirus disease, especially in developing countries where breast feeding frequently continues past the sixth month of life when rotavirus diseases are most common.

Factors such as climate, density of population, or local habits also influence the incidence of rotavirus infection. However, as precise data are not available, the role played by these factors in the transmission of the disease is still a matter of speculation. The true role and relative importance, if any, of water, food, air, and fomites in transmission still needs to be elucidated.

**Environmental Aspects**

Studies conducted on rotavirus have indicated relatively heat-resistant properties. It has been discovered that rotavirus infectivity is rapidly lost on treatment with 5 mM of either EDTA or EGTA. On the other hand, a number of chemical disinfectants have been found to be relatively ineffective in the inactivation of rotavirus suspended in fecal matter.

In comparison with certain enteroviruses, rotavirus seems to have a lower capacity to absorb a variety of soil types, aluminum hydroxide, and activated sludge floes. This, together with their relative resistance to chlorine, suggests that conventional methods of water and sewage treatment may be relatively less effective for the removal and inactivation of rotavirus.

Rotavirus has also been detected in raw and treated sewage and fecally-polluted waters. Samples of drinking water collected in Egypt and Mexico have been found to contain viable rotavirus particles.

More research is needed on factors that influence the survival of rotaviruses in the environment, both in the community at large and within closed communities such as hospital wards, day care centers, and nursing homes. In addition, the true role and relative importance of water, food, air, and fomites as vehicles in the spread of rotavirus infection require future research.

**Bibliography**

Report of the Second Meeting of the Scientific Working Group on Viral Diarrheas: Microbiology, Epidemiology, Immunology, and Vaccine Development (Geneva, 1-3 February 1982).


(Source: Enteric Disease Control Program, Communicable Diseases Control, Division of Disease Prevention and Control, PAHO.)
Bolivian Hemorrhagic Fever

The disease was first identified in 1962 during an outbreak that caused a large number of deaths in the agricultural community of Orobayaya, Province of Iténez, Department of Beni, which was abandoned by its 600 inhabitants. Subsequently, an even larger outbreak occurred in San Joaquín, the capital of the Province of Mamoré, also in the Department of Beni, and was the subject of an in-depth study by Bolivian personnel and by the personnel of the Middle America Research Unit (MARU) of the United States Public Health Service.

The incubation period of Bolivian hemorrhagic fever is from 7 to 14 days. Direct transmission by nasopharyngeal secretions was confirmed in at least two of the cases. Onset of the disease is gradual. From the beginning, high and sustained fever and myalgia are usually present. About 30 per cent of the patients have hemorrhages from the third day onward. Half the cases show hypotension and tremors of the tongue and hands from the fourth to the sixth day. Leukopenia, as well as thrombocytopenia, are invariably present.

Most cases occur during the dry season and at the peak of agricultural activity—the pattern demonstrated by the outbreaks in Orobayaya and San Joaquín. The disease attacks persons of all ages and of both sexes.

Morbidity is usually high; in San Joaquín it exceeded 30 per cent of the total population. The highest mortality occurs among the very young and the very old.

In 1963 the etiologic agent—the Machupo virus—was isolated both from human and animal tissues and the rodent *Calomys callosus* was identified as the reservoir of the virus. The San Joaquín outbreak was brought under control by exterminating this rodent. Later outbreaks in hamlets and farms were also associated with the presence of *C. callosus* in the victims’ houses and in their immediate neighborhood. However, in 1971 an outbreak occurred in a hospital in Cochabamba, a city situated outside the endemic area of the disease. The index case appeared to have contracted the infection on a ranch located in the community of Fortaleza, Province of Yacuma, Department of Beni. Five of the persons that were in contact with the patient during his stay in the hospital contracted the disease and four of them died.

Thus far it has not been possible to isolate the virus from any other animal species but *C. callosus*, its natural host. Between 1963 and 1966 the MARU research workers in Panama delimited the approximate area of dispersion of this rodent in Bolivia, which, in the Department of Beni, includes the Moxos plains; in the Department of Santa Cruz, the entire eastern and southeastern region, except for a strip that runs north to south and includes the foothills of the Mato Grosso; in the Department of Cochabamba, the northern part of the Province of Chapare; in the Department of Chuquisaca, the Province of Luis Calvo; and in the Department of Tarija, the Province of Gran Chaco. The total area involved is approximately 500,000 km².

The Machupo virus has been detected in *C. callosus* captured in the Provinces of Iténez, Mamoré, and Yacuma in the Department of Beni (an area of approximately 27,433 km² as a whole). In the Province of Velasco, Department of Santa Cruz, these rodents have been found to be infected with the Latino virus (Machupo II), which is an arenavirus apparently nonpathogenic for man.

In the experiments carried out, the Machupo virus did not produce acute disease in *C. callosus* of any age, regardless of the route of inoculation used. In sucklings, the virus multiplied rapidly in the lymphatic ganglia and the spleen, and between 7 and 10 days later was found in all the tissues (including the brain), and in blood, oral swabs, and urine. The infected animals did not grow as rapidly as their controls, but it is interesting to note that they showed chronic infection accompanied by persistent viremia and never demonstrated circulating antibodies.

In other investigations, adult *C. callosus* inoculated with Machupo virus responded in two ways: with chronic viremia, splenomegaly, and no antibodies, or without viremia (although the virus was present in the urine, buccal cavity, and other tissues), without splenomegaly, and with neutralizing antibodies two or three months after inoculation.

The presence of splenomegaly in infected *C. callosus* is an interesting characteristic that is observed from the second week after onset of the infection and appears to persist for many months. In the course of one epidemic, it was found that the weight of the spleen of those rodents was an important indicator of infection by Machupo virus. Spleens of more than 0.25 g were positive. However, no virus was found in more than half the spleens that weighed between 0.20 and 0.25 g and in none of those that weighed less than 0.20 g.

Taking into account the diagnostic techniques available in recent years, the criterion used in field work has been to consider all cases of splenomegaly in *C. callosus* as an indicator of suspected infection; unfortunately, confirmation in these cases has not been possible. The percentages of suspected infection ranged from 55 to 93 per cent.

No human cases of Bolivian hemorrhagic fever have been registered since 1974.

(Source: Boletín Epidemiológico, Ministry of Social Welfare and Public Health, Bolivia, Number 75, 1981.)

Editorial Comment

Since the program to control *Calomys callosus*, no addi-