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Clinical Microbiology Newsletter

Vol. 2, No. 5 March 1, 1980

 ISSN 0196-4399

Human Rotavirus Gastroenteritis

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For at least three decades, attempts have been made to demonstrate a specific viral etiology for the 75% of cases of gatstroenteritis not attributable to known bacterial pathogens. Early cultural studies frequently demonstrated the presence of enteroviruses or adenoviruses in stool, but their significance remained obscure because of a high rate of recovery in control subjects without diarrhea (5, 22, 24).

Reovirus-like particles were first associated with diarrheal disease in humans by Bishop et al. (3), who in 1973 observed the virions, by electron microscopy, in duodenal biopsy specimens from six of nine children with gastroenteritis. This study followed the 1972 report by Kapikian et al. (9) that a virus, morphologically similar to parvoviruses, was associated with an outbreak of gastroenteritis among children and adults in Norwalk, Ohio. In subsequent years, electron microscopy of diarrheal stool has suggested the association of a number of other morphologic categories of viruses with diarrhea in humans; these include "astrovirus" (12, 19), "minirotavirus," and "calicivirus" (23), coronavirus (19), and a serologically identified subgroup of noncultivable adenoviruses (7). However, the parvovirus-like agents ("Norwalk agent") and the rotavirus are the only two viruses that have been demonstrated clearly to have a causal role in human gastroenteritis. The former is associated with well-defined outbreaks among adults and older children. Rotavirus is responsible for a substantial amount of acute diarrheal illness in children throughout the world and is the subject of this review.

Historical Background

The initial report, by Bishop (3), of reovirus-like virions within the endoplasmic reticulum of duodenal epithelial cells of children with diarrhea, in Melbourne, Australia, was rapidly confirmed by other workers. Flewett et al. (6), working in Birmingham, England, observed similar particles in diarrheal feces; and Middleton et al. (16), in Toronto, Canada, found the virions in fecal specimens, duodenal aspirates and biopsies, and autopsy specimens of the upper jejunal mucosa. The virus appeared morphologically similar to reoviruses and has been variously referred to as human reovirus-like agent (HRVLA), orbivirus, duovirus, and most commonly as rotavirus. Beginning in 1969, rotaviruses had been found associated with diarrheal disease in the infants of a number of animal species, including calves, piglets, lambs, foals, and mice (15).

Description of the Virus

The term rotavirus is descriptive of the wheel-like appearance of the double-shelled virion, with the inner layer of capsid subunits forming "spokes" and the outer layer a smooth rim (in contrast to the icosahedral outer edge of reoviruses). The rotavirus virion measures about 70 nm in diameter and contains double-stranded RNA. Rotaviruses from different animal species vary with respect to the electrophoretic mobility of their RNA segments on polyacrylamide gels. Differences are also demonstrable between the polyacrylamide-gel profiles of the outer, but not the inner, capsid-layer polypeptides. This observation supports the demonstration of a group antigen associated with the inner capsid, while the outer shell apparently contains species-specific antigens. An excellent review of work done to date in characterizing rotaviruses has been provided by McNulty (15). Figure 1 shows a porcine rotavirus as viewed by immune electron microscopy.

Adaptation of rotaviruses to growth in cell culture is difficult and has been accomplished with varying degrees of success for several of the animal rotaviruses (15). Wyatt et al. (26) very recently reported cultivation, through 14 serial passages in cell culture, of a human-rotavirus isolate.

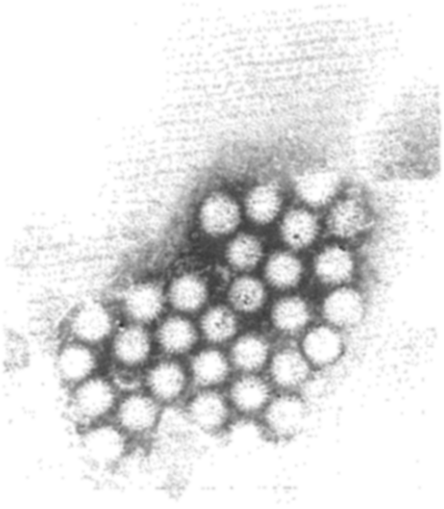

Fig. 1. Porcine rotavirus as viewed by immune electron microscopy. Most of the virions lack the smooth outer shell; a portion of an "empty" broken capsid is also visible. Negatively stained with phosphotungstic acid, X100,000. Courtesy of J. G. Lecce and M. W. King.

This was accomplished after 11 passages in gnotobiotic piglets, and after using trypsin treatment of the virus and centrifuging the inoculum onto the monolayers. Fortunately, antigenic cross-reactivity allows utilization of cultivable animal rotaviruses for production of diagnostic antisera capable of detecting human rotavirus.

Two serotypes of human rotavirus are recognized (30). Type 2 apparently is involved in about 75% of symptomatic infections in various countries and may be more virulent; immunity is not cross-protective (29). Most children acquire antibody to both types by the age of 2 years, and most samples of breast milk contain antibody to both serotypes (29).

Clinical Syndrome

The prevalence and typical clinical features of rotavirus gastroenteritis have been described by several authors (14, 11, 8, 1). The disease most commonly affects children between the ages of six months and two years, and rotavirus accounts for at least half of those children hospitalized because of diarrhea. In temperate climates the incidence peaks in the winter months and is rare in the warm season; Kapikian et al. (8) detected rotavirus in 78% of 27 children hospitalized for diarrhea during December and January and in none of 41 admitted during May through October. The incubation period is about one to three days.

The disease is characterized by acute onset of diarrhea lasting about four to eight days. Vomiting is mentioned in most studies as a prominent feature of the illness; it is often the initial symptom and may occasionally be present in the absence of diarrhea. Wyatt et al. (26) reported that vomiting was four times more common in children infected with rotavirus than in those with diarrhea of other etiology. Dehydration is the most common reason for hospitalization of these patients and is much more frequent in rotavirus infection than in other diarrheal illnesses (26). Fever and lymphocytosis may or may not be present. A respiratory prodrome or evidence of otitis media was observed by Lewis et al. (14) in 66% of children with rotavirus infection; this was at least twice the frequency observed in children with other diarrheal illnesses, although the rate of isolation of respiratory viruses was not different. Respiratory symptoms have previously been associated with rotavirus infection in animals.

Although rotavirus gastroenteritis is usually self-limiting, 21 fatal cases, in Toronto, have been described by Carlson et al. (4) These deaths occurred within two to three days of onset and generally resulted from rapidly progressive dehydration in previously well-nourished children.

Most studies of the incidence and symptoms of rotavirus gastroenteritis have been concerned with hospitalized patients. A three-year longitudinal study of 24 Guatemalan children (27) identified rotavirus in 14.2% of nonbacterial diarrheal episodes and confirmed the frequent occurrence of vomiting and dehydration in this as opposed to other diarrheal illnesses.

Rotavirus in Adults

Several studies (8, 10, 25) have documented that rotavirus infection (rarely symptomatic) occurs in 30 – 40% of adult-family contacts of children with rotavirus gastroenteritis. This subclinical or mild symtomatic infection may occur in the presence of complement-fixing serum antibody.

Neonatal Infection

Shedding of rotavirus in stool is fairly common among neonates, but symptomatic illness is rare (18). On the other hand, endemic rotavirus infection is much more likely to be symptomatic in babies requiring special care than in healthy full-term infants; such outbreaks are difficult to control because rotavirus appears in the stool as much as three days before onset of symptoms (2). The grouping of infants together in a nursery and frequent handling by unrelated adults has been associated, by Bishop et al., with rotavirus diarrhea (2); some interesting parallels exist between these observations and a rearing regimen found, by Lecce et al. (13), to foster rotavirus diarrhea in piglets. The apparently lower virulence of rotavirus for healthy neonates than for older infants is unexplained. A role for breast-milk antibody has been postulated (29, 13); it is of interest that colostrum deprivation greatly increases susceptibility in newborn ungulates (13).

Immunodeficient Patients

A recent report (1) described rotavirus infection in four children with primary immunodeficiency diseases, who had diarrheal episodes. Two of these children had chronic, symptomatic infection with excretion of rotavirus for more than six weeks. Rotavirus antigen was detected by an enzyme-linked immunosorbent assay (ELISA) in serum from two of the patients, as well as in their stools.

Therapy

Dehydration is the major symptom which may require therapy. It has been demonstrated, in Bangladesh, (20) that oral hydration with sucrose or glucose electrolyte solutions is a suitable alternative to intravenous-fluid therapy in rotavirus diarrhea.

Laboratory Diagnosis

Until recently, detection, by electron microscopy, of rotavirus particles in stool was the major method used for the diagnosis of current infection. Negative staining is suitable for this purpose, and aggregation of the virions with antiserum (immune-electron microscopy) facilitates their detection and specific identification. A cell-culture method has been described (17) in which trypsin-treated fecal extracts, containing rotavirus, produced antigen in cell monolayers that was detectable by immunofluorescence, although progressive infection did not occur. Recently, ELISA for human-rotavirus antigen in stool suspensions has been described (28). This assay has a sensitivity at least equal to electron microscopy, and it can be performed in a total of four hours and read visually. This method has also been used for serodiagnosis. Marketing of a commercially produced kit for

rotavirus ELISA (Abbott Laboratories) is planned soon.

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