

NONBACTERIAL GASTROENTERITIS¹

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Two distinct types of virus have been implicated as agents of nonbacterial gastroenteritis. One, 27 nm in diameter, is associated with a brief acute epidemic illness. The other, 70 nm, has been identified as the agent most frequently responsible for infant nonbacterial diarrhea.

Significant advances have recently been made in elucidating the etiologic agents of acute, infectious, nonbacterial gastroenteritis. This disease complex, which affects a broad range of the human population, is thought to be an important cause of death among infants and young children in tropical areas and in developing countries. It was also the second most common disease recorded in a Cleveland family study that included some 25,000 illnesses and spanned a period of about 10 years.

The 27-nm Virus

Two distinct types of viruses have been implicated in nonbacterial gastroenteritis, one of which has a diameter of approximately 27 nm. Initially virus-like particles were observed in the stools of individuals infected with the Norwalk agent, a filterable, transmissible agent obtained during and outbreak of acute, nonbacterial gastroenteritis at a school. This outbreak was typical of the epidemic form of nonbacterial gastroenteritis. The attack rate was high among students, teachers, and family contacts, and individuals of all ages were involved. Epidemic, acute, nonbacterial gastroenteritis typically has a short incubation period (one to two days) and a short

duration of illness (also one to two days). The disease is self-limited; the symptoms include nausea, vomiting, diarrhea, abdominal pain, malaise, and/or low-grade fever.

The Norwalk agent was visualized by immune electron microscopy (IEM). It was shown to have a diameter of approximately 27 nm and a buoyant density of 1.38-1.41 gm/cm³. The latter property indicated that it resembled a parvovirus more closely than a picornavirus. Individuals who were ill during the Norwalk outbreak, as well as volunteers who became ill following experimental infection, developed a serologic response to the 27-nm virus, suggesting that it was the etiologic agent of the outbreak. Support for this view also came from the close temporal association of the illness and the presence of 27-nm particles in stools in the course of experimental infection.

Virus particles resembling the Norwalk agent in size and buoyant density were also visualized by IEM in stool filtrates derived from two of six other outbreaks of transmissible nonbacterial gastroenteritis. In both cases these particles were present at a lower concentration in the stool than the Norwalk agent had been, and they were detectable by IEM only after the stool filtrates were concentrated. The two viruses were antigenically distinct. One of them, however, shared antigenic determinants with the Norwalk agent. Thus there appear to be at least two serotypes among the 27-nm gastroenteritis viruses. To date all efforts to grow the 27-nm viruses in vitro have failed.

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The 70-nm Virus

The syndrome of infantile gastroenteritis differs from the epidemic form of the disease in a number of ways. For example, the attack rate is very low among family contacts of patients with infantile diarrhea. The virus responsible for a significant proportion of nonbacterial diarrheal illnesses during infancy also differs from the viruses which have been implicated in the epidemic form of the disease. It is now clear that the main pathogen of infantile diarrhea is a 70-nm virus (variously designated as a duovirus, rotavirus, or reovirus-like agent) which morphologically resembles the reoviruses and orbiviruses. In contrast, 27-nm virus particles have been detected infrequently in the infantile diarrhea syndrome and their etiologic role has not been established.

During the past two years the 70-nm virus has been associated with infantile diarrhea throughout the world, wherever appropriate gastrointestinal biopsy or stool specimens have been examined by electron microscopy. Over all, the particle has been detected in approximately 40 per cent of the cases of infantile diarrhea studied; during the winter months, when infection appears to be most common, the frequency of detection has averaged 70 per cent, and during the peak of the winter outbreak the virus has been observed in specimens from 80 to 90 per cent of the infants and young children hospitalized with diarrhea.

The 70-nm virus has been grown in monolayer tissue culture and in organ cultures of human fetal intestine. Thus far growth in the former system has been relatively poor. Antibody to the virus can be assayed by indirect immunofluorescence (IF) using frozen sections of infected intestinal organ culture as antigen. In addition, certain stool filtrates which contain a high concentration of the virus

can be used as a complement-fixing (CF) antigen for serologic study of the infection. It has been found that approximately 80 per cent of the young diarrhea patients with particles detectable in their stools develop a serum CF antibody response. The IF technique appears to be even more sensitive for serodiagnosis. Since most stool filtrates containing virus particles do not contain enough antigen to fix complement, other sources of antigen have been explored. The Nebraska calf diarrhea virus (NCDV), which can be cultivated in tissue culture and which is antigenically related to the human virus, has been found suitable for this purpose. NCDV tissue culture concentrates have fixed complement with antibody in human sera, and the antigen has been found 75 per cent as efficient for serodiagnosis of infection as the human virus antigen.

Serologic surveys (IF and CF) performed in the Washington, D.C., area to determine the prevalence of antibody to the 70-nm virus indicate that infection with the virus has been widespread over the past 15 years. The surveys found that 60 per cent of the infants studied were infected by the end of the first year, that most children were infected by the end of the second year, and that few children escaped infection until they were four years of age.

Efforts to induce disease in experimental animals with the 70-nm virus met with success during 1975. Newborn piglets, calves, and rhesus monkeys all developed diarrheal illness after being given a human stool filtrate containing the virus.

Finally, it has been shown that the human virus is related antigenically to NCDV, to the virus of epizootic diarrhea of infant mice, to the SA 11 virus of monkeys, and to the O virus of sheep. It is of interest that three of the viruses in this closely related group cause gastroenteritis in the natural host.

SUMMARY

Significant progress has been made toward determining the agents of acute, infectious, nonbacterial gastroenteritis. Two distinct types of viruses have been implicated. One of these, a particle about 27 nm in diameter, is involved in the acute epidemic form of the disease of short duration. The other, a 70-nm virus, is rarely involved in acute epidemic gastroenteritis, but it has been associated worldwide with infantile

diarrhea and is responsible for a considerable proportion of all nonbacterial diarrheal illness in infants. Experiments with the 70-nm virus have induced disease in newborn piglets, calves, and rhesus monkeys. In addition, this human virus has been antigenically related to four other viruses, three of which cause gastroenteritis in their natural animal host.