Education

Skin manifestations with *Rotavirus* infections

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Abstract

Rotavirus infection is one the most frequent cause of diarrhea among infants and children. Although it is not associated to specific dermatologic clinical pictures, recently, different clinical manifestations have been reported in association with this infection. They include exanthema, Gianotti–Crosti syndrome, and Acute Infantile Hemorrhagic Edema. The condition can be diagnosed microbiologically with stool cultures. The prognosis is excellent in healthy, immunocompetent individuals.

Introduction

Rotaviruses are classified with the Reoviridae family. They have a genome consisting of 11 double-stranded RNA segments and present a characteristic wheel-like appearance when viewed by electron microscopy (the name rotavirus is derived from the Latin rota, meaning "wheel").

Rotavirus shows genetic and antigenic diversity, in particular six serological groups have been identified, three of which (groups A, B, and C) infect humans. Group A rotavirus is endemic worldwide. It is the leading cause of severe diarrhea among infants and children, and accounts for about half of the cases requiring hospitalization. In temperate areas, it occurs primarily in the winter, but in the tropics it occurs throughout the year. Group B rotavirus has caused major epidemics of severe diarrhea affecting thousands of persons of all ages in China. Group C rotavirus has been associated with rare and sporadic cases of diarrhea in children in many countries. In addition to the well-known typical clinical manifestations which is gastroenteritis, dermatologic involvement such as exanthems,[1] Gianotti–Crosti syndrome,[2,3] and recently infantile acute hemorrhagic edema[4] has been reported in association with *Rotavirus* infection.

Epidemiologic Characteristics

Rotavirus is recognized as the most common cause of severe gastroenteritis in children below 5 years of age throughout the world, with an estimated 140 million cases of gastroenteritis and 800,000 deaths in children between the ages of 6 months to 2 years in developing countries.[5]

The primary mode of transmission is fecal-oral, mostly after ingestion of contaminated water and food, although some have reported low titers of virus in respiratory tract secretions and other body fluids. The infective dose is presumed to be 10–100 infectious viral particles. Because a person with rotavirus diarrhea often excretes large numbers of virus (108–1010 infectious particles/ml of feces), infection doses can be readily acquired: person-to-person spread through contaminated hands is probably the most important means by which rotaviruses are transmitted in close communities such as pediatric and geriatric wards, day care centers and family homes. Infected food handlers may contaminate foods that require handling and no further cooking, such as salads, fruits, and shell fish. Because the virus is stable in the environment, transmission can occur through ingestion of food or contaminated water, in particular closed water sources as cruise ships and airplanes are commonly responsible for rotavirus infections. Rotavirus can be transmitted by fomites as well as it is a hardy virus. Sanitary measures adequate for bacteria and parasites seem to be ineffective in endemic control of rotavirus, as similar incidence of rotavirus infection is observed in countries with both high and low health standards. In addition, asymptomatic rotavirus excretion has been well documented and may play a role in perpetuating endemic disease. Most cases of rotavirus infections are actually asymptomatic.

Clinical Description

Gastroenteritis

The incubation period for rotavirus disease ranges from 1 to 3 days. *Rotavirus* gastroenteritis is a self-limiting, mild to severe disease characterized by vomiting, watery, green, foul-smelling diarrhea for 3–8 days and low-grade fever. Symptoms often start with vomiting followed by 4–8 days of diarrhea; abdominal pain occur frequently. The latter can be so pronounced in some children such as appendicitis and abdominal obstruction need to be ruled out. Although the infection can

be symptomless, severe, and often life-threatening illnesses for necrotizing enterocolitis, hemorrhagic gastroenteritis, dehydration can occur. Rotavirus replicates in mature villus enterocytes in the small intestine and in immunocompetent persons, the infection is limited in the gut. However, reports of rotavirus RNA in the cerebral spinal fluid and serum of children infected with rotavirus suggest the possibility that rotavirus escapes the intestine into the circulatory system, resulting in antigenemia and possible viraemia.[6] Renal and hepatic involvement can be prominent in immunocompromised patients. Rotavirus also induces both local and systemic immune responses. Immunity after infection is incomplete and reinfections occur in persons of all ages. Antibodies seem to protect against rotavirus infection but cell-mediated immune responses are probably also important for protection. Strong T-cell responses to rotavirus are transient and the ability to respond usually disappears in 1 year. In adults, T-cell responses to rotavirus are strong, implicating that several infections are needed to develop consistent, strong T-cell responsiveness.[7] This could explain the less severity of repeat infections with respect to the original infection.

Exanthema

A generalized maculopapular exanthem possibly related to rotavirus was described by Ruzicka *et al*. in 1985,[1] in a 28-year-old man who presented signs of hepatitis. The patient's serum contained rotavirus antibody at titers of 1 : 256 and 1 : 512. One week before, his two sons had suffered from rotavirus gastroenteritis.

Gianotti–Crosti syndrome (GCs) or papular acrodermatitis of childhood (PAC)

Gianotti–Crosti syndrome (GCs), also known as papular acrodermatitis of childhood (PAC), is a self-limited disorder with acute onset generalized lymphadenopathy and monomorphic lentil-sized, dense, nonconfluent, symmetric, flat-topped, nonpruritic papules. The histopathologic findings are nonspecific and include focal parakeratosis, mild spongiosis, superficial perivascular infiltrate, papillary dermal edema, and extravasated red blood cells. It is considered a nonspecific cutaneous host response to a variety of infectious agents, particularly viruses.[8–10]. Epstein–Barr virus, hepatitis B virus, cytomegalovirus, adenovirus, coxsackievirus, parainfluenza virus, and more recently poxvirus, parvovirus B19, and herpesvirus 6 have been associated with this distintive exanthem. In 1988, Patrizi *et al*. reported the first two cases of GCs associated to rotavirus infection.[2] A new case was observed in 1998 by us, confirming the possibility of such association.[3]

Infantile acute hemorrhagic edema (AHE)

Acute hemorrhagic edema (AHE) is a distinctive cutaneous disorder characterized by large rosette-shaped purpuric lesions on the face and limbs and acral edema accompanied by fever, occurring almost exclusively in children between the ages of 4 months and 2 years during winter. Spontaneous resolution normally follows within 3 weeks. The nosologic position regarding the disease is still debated. Although some consider AHE a purely cutaneous variant of purpura of Schönlein Henoch (HSP), it is actually regarded as a separate clinical entity among cutaneous small vessel vasculitis of childhood. Numerous studies suggest AHE is an immune-mediated vasculitis in response to a variety of antigenic stimuli. Most patients have a history of recent infection, drug administration, or immunization.[11] The most reported infective agents are staphylococci, streptococci and among viruses, *Adenovirus*, but many other agents, such as *Escherichia coli*, *Mycobacteria*, *Coxsackievirus*, *Campylobacter mucosalis*, have been reported in association with cases of AHE. A case of AHE occurring in an 11-month-old patient presenting gastrointestinal symptoms has recently been related to *Rotavirus* infection.[4]

Diagnosis

Because an extremely high number of virus particles are present in the feces during the acute gastroenteritis, specific diagnosis of the disease is made by identification of the virus in the patient's stool. Latex agglutination and in particular enzyme immunoassay (EIA) is the test most widely used to screen clinical specimens. Electron microscopy and polyacrylamide gel electrophoresis are used in some laboratories in addition or as an alternative to EIA. A reverse transcription polymerase chain reaction has been developed to detect and identify all three groups of human rotaviruses.[12] Negative differential diagnostic indicators are the presence of blood cells or white blood cells in the stools, as these are characteristically absent in rotavirus diarrhea.

Prevention

Hand washing is the main method of decreasing transmission, as well as the confinement like the child should stay home from daycare or school. Efforts to develop safe and effective vaccines resulted in licensure of the first live oral vaccine, tetravalent, rhesus-based rotavirus vaccine (RRV-TV), which was incorporated into the U.S. immunization schedule in 1998. The recommended dosing schedule was 2, 4, and 6 months of age. Less than 1 year later, however, the vaccine was withdrawn when reports of cases of intussusception in children were linked to recent or current vaccination. The risk of intussusception following Rotashield immunization is estimated to be between 1 in 10,000–1 in 32,000 vaccinees and is highest during the 3–14 days following the first dose of vaccine. Infants older than 3 months at the time of the first dose of vaccine are at increased risk of intussusception.[13] One vaccine was licensed in Mexico in 2004 and a second has completed clinical trials in the United States and Europe and may be licensed within the next years.

Prognosis

Recovery is usually complete. However, severe diarrhea without fluid and electrolyte replacement may result in severe diarrhea and death. Children 6 months to 2 years of age, premature infants, the old people, and the immunocompromised are particularly prone to more severe symptoms caused by infection with group A rotavirus.

Management

The dermatologist must be aware about the possibility that skin manifestations, as GCs, AHE, and other maculo-papular exanthema, can be associated to rotavirus infection.

Rehydration and maintaining nutrition are recommended ways for the treatment of rotavirus diarrhea. The lack of maintaining these factors is the main cause of morbidity and mortality in the developing countries. Childhood mortality caused by rotavirus is relatively low in the developed countries, with an estimated 100 cases/year in the U.S., but reaches almost 1 million cases/year worldwide. Mortality has not declined and association with other enteric pathogens may play a role in the severity of the disease. Current efforts are targeted at the development of suitable vaccines and the implementation of infection control measures.

Economic impact

The estimated number of hospitalizations attributed to rotavirus infection has increased,[14] thus there is a great impact of rotavirus acute gastroenteritis, mainly of nosocomially acquired infection, on medical health care costs worldwide. Additional large economic impacts on industry and productivity in the work force is related to days lost from work and school. To cut costs, efforts in disease prevention should be encouraged. In particular, a safe and effective vaccine could reduce morbidity and be advantageous by allowing redeployment of healthcare resources to other critical areas.

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