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Feature Articles: Rotavirus infection in Asia

Foreword

HIROSHI USHIJIMA

Department of Developmental Medical Sciences, Institute of International Health, Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

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Acute viral gastroenteritis is caused mainly by rotavirus, followed by calicivirus, enteric adenovirus and astrovirus in order. Their frequencies in Japan are about 50, 30, 10 and 10%, respectively, and change between areas and years.[1] Enterovirus, coronavirus, cytomegalovirus, influenza virus, Aichivirus and so on are also agents of acute viral gastroenteritis. Usually rotavirus occurs in late winter (February and March) and calicivirus in early winter (November and December). However, food poisoning caused by calicivirus occurs in adults in December, January and February.[1] Here, the recent trend of rotavirus gastroenteritis is described.

Epidemiology of rotavirus infection

Human rotaviruses are classified into groups A, B and C. Almost all human rotaviruses belong to group A. Group C rotaviruses are often discovered in a few percent of patients in Japan.[2] Group B rotavirus spread in more than 10 000 people in China from 1982 to 1983.[3] It was also recognized in five cases in India from 1997 to 1998.[4] Japanese people do not have antibody against group B rotavirus, so if it comes into Japan it may spread broadly. Antibody against group C rotavirus increases in higher age groups than antibody against group A rotavirus. Nowadays, more than 90% of G types (VP7 types) of group A rotaviruses in Japan are G1. However, from 1980 to 1990, the sum of G2, G3 and G4 rotaviruses was 30–40%. Type G9 was found quite rarely at that time.[1] Type G5 rotaviruses have been reported in Brazil[5] and G9 rotavirus has been reported as 10–20% of rotaviruses in the USA.[6] These recent phenomena show that the G types other than G1–G4 could spread world wide. P types (VP4 types) are also important for sero-epidemiologic analysis. G types are divided into 14 types and P types are divided into 20 types in human and animal rotaviruses. The main combinations of G types and P types are G1P[8], G2P[4] and others; however, some new recombinants appear in field studies.[7] Reassortment, recombination and mutation will appear naturally in rotavirus infections.[8] There are some minor rotavirus serotypes, G5, G8, G9 and G12. If humans do not have protection (cellular immunity and serum antibodies) against those rotaviruses, the viruses will spread quite quickly in the world. Type G9 may be one example of this.[6,9–11]

Correspondence: Hiroshi Ushijima MD, Department of Developmental Medical Sciences, Institute of International Health, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.
Email: ushijima@m.u-tokyo.ac.jp
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Rotavirus vaccine

Diarrheal diseases are an important public health problem, particularly in developing countries. Rotavirus is the most common causative agent. It causes death of approximately 870 000 infants and young children and 18 million moderate to severe episodes of diarrhea per year in children younger than 5 years of age in developing countries.[12] While the estimated annual mortality due to diarrhea has decreased, the mortality remains between 480 000 and 640 000.[13]

Nowadays in Japan, approximately 100 000 infants per year visit outpatient clinics due to acute gastroenteritis. The number is the same as the number of births. Although rotavirus, enteric adenovirus, calicivirus and astrovirus are main causes of gastroenteritis, approximately 40% of severe gastroenteritis is caused by rotavirus.[14]

An oral rotavirus vaccine was developed and used in infants in 1998 and 1999 in the US under the approval of the Food and Drug Administration. The method of this tetravalent vaccine has been called a ‘modified Jennerian approach’ because the VP7 gene of Rhesus rotavirus (RRV MMU18006 strain, G3) was replaced by those of G1, G2 and G4 human rotaviruses. Other genes of the vaccine are from strain MMU18006.[15] This vaccine has the same immunogenicity as human natural rotaviruses, but has low pathogenicity. This vaccine can decrease severe rotavirus infection in 80–90% of patients and total rotavirus infection in 50%. Diarrhea caused by rotavirus is approximately

10–30% of total diarrhea cases, so rotavirus vaccine may inhibit diarrhea. Even if infants take the vaccine, it does not always stop rotavirus diarrhea but reduces the symptoms. Side-effects of mild diarrhea, nausea and fever are often seen. From this point of view, the introduction of rotavirus vaccine needs effort to convince parents of the effects of the vaccine in comparison with measles, mumps, varicella and rubella vaccines. Rotavirus vaccine is used together with poliovirus vaccine orally. However, due to the occurrence of intussuseption by the developed vaccine, the Center for Disease Control and Prevention has advised postponing use of the vaccine[16] and the vaccine company has been obliged to withdraw it from the market. Other approaches for rotavirus vaccine have also been examined: rotavirus genome DNA (DNA vaccine)[17] and virus-like particles produced by genetic engineering have been studied. They are used intramuscularly, subcutaneously and orally. Killed rotavirus vaccine has also been studied.

To develop and introduce rotavirus vaccine, the cost-effectiveness of the vaccine was calculated in United States and its benefit valued. In Japan, the medical expense of inpatients and outpatients with rotavirus infection has been estimated at 10 100 million yen and 1600 million yen, respectively. These costs make it valuable to introduce rotavirus vaccine into Japan from medical and economic points of view.[18]

Rotavirus and pathogenesis

Rotavirus grows mainly in the epithelial cells of the small intestine. Trypsin is not needed to infect rhesus rotavirus into cells but is needed to infect human rotavirus. The VP4 is cleaved to VP5 and VP8 by trypsin. VP8 is a ligand against cell receptor. Sialic acid is a receptor but another receptor may also be used.[19] After rotavirus infects the cells, replication of virus RNA and the synthesis of structure and non-structure proteins occurs in cytoplasm. Non-structure protein 4 (NSP4) contains a structure called 'enterotoxin'.[20] This protein accumulates Ca ions inside the cells and induces apoptosis. Although some other mechanism exists for the production of diarrhea, enterotoxin increases the outflow of Cl ions from cells and reduces absorption of Na ions and H_2O into cells, finally inducing diarrhea.[20]

Rotavirus infection and complications

Rotavirus infection causes diarrhea, vomiting and fever of acute gastroenteritis. The virus may also cause chronic gastroenteritis and hepatitis in immunocompromised children.[21] Furthermore, rotavirus gastroenteritis associated with convulsions or encephalopathy, as well as rash, has been observed in non-immunocompromised patients.[22,23] The incidence of convulsions associated with rotavirus gastroenteritis in Japan, Taiwan, and India was 2.9, 5.3 and 3.7%, respectively.[24] However, convulsions are not commonly associated with rotavirus gastroenteritis in the USA. Rotavirus RNA was detected not only from stool samples, but also from sera, cerebrospinal fluid and throat swabs. From sequence analysis of the VP7 gene in stools, sera, cerebrospinal fluid and throat swabs, there were no appreciable differences in viral sequences between samples from cerebrospinal fluid, sera or stools.[25] Recently, 3 years of data from 1996 to 1998 in Japan at hospitals equipped with more than 100 beds showed that 40 996 (9.9%) of 415 670 inpatients in children's wards were admitted with gastroenteritis. Rotavirus, adenovirus and calicivirus were found in 16.3, 0.01 and 0.03%, respectively, of all inpatients with gastroenteritis. The most common complications, in order, were hepatitis/disorder of liver function (3.0%), convulsion (1.7%), encephalitis/encephalopathy (0.1%) and pneumonia (0.04%). Other complications of rotavirus infection were intussuseption (two cases), paralytic ileus (six cases), protein-losing enteropathy (one case), Gianotti syndrome (one case), appendicitis (one case), idiopathic thrombocytic purpura (one case), transient infantile hyperalkaline phosphatasemia (two cases) and infectious mononucleosis (one case). These results obtained from general hospitals and physicians did not always include examination of viruses in inpatients. The results may be lower than those that were examined at hospitals with specialists.

Conclusion

General views on the epidemiology, vaccine, pathogenesis and complications of rotavirus infections were described in this foreword. More details of epidemiology, diagnosis and treatment of rotavirus infection are described in this special feature by my colleagues in Asia.

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