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Ohio (USA) State University,
Lab. Gastroenteritis Virales -
Inst. C. Malbrán e
Inst. de Virología - INTA
Castelar



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Rotaviruses: Zoonotic potential and adaptation to new hosts

Linda J. Saif, PhD
Food Animal Health Research Program
Ohio Agricultural Research and Development Center
The Ohio State University
Wooster, OH 44691- USA

Abstract

Group A rotaviruses are a leading cause of dehydrating diarrhea in children and also cause diarrhea in young animals worldwide. Nongroup A rotavirus infections (B and C) have also been documented in humans, cattle and swine. Recent data is emerging that some common animal group A rotavirus P or G serotypes (VP4, P types or VP7 G types) may occur in humans, especially in developing countries where there may be close contact between animals and young children. Both symptomatic and asymptomatic infections with such strains may occur, but initially many such infections may be subclinical. Although the predisposing factors for transmission of animal rotavirus strains to humans or vice versa are unclear, mixed infections of children or animals by animal/human strains play a role in

generation of new reassortant strains with animal/human P or G types. In addition recent evidence indicates that mixed infections of humans, swine and cattle with group A and group C rotaviruses occur. Experimental studies of dual group A/C rotavirus infections in calves have shown that coinfection of calves with a bovine group A rotavirus enhanced the fecal shedding of a bovine group C rotavirus. The latter virus was genetically more closely related to porcine than to bovine group C rotaviruses suggesting that dual infections may play a role in the adaptation of heterologous rotaviruses to new host species by enhancing their shedding and host-to-host transmission. The mechanisms involved are unknown, but important to define to better understand rotavirus evolution, transmission and adaptation to new hosts.

Introduction

Rotaviruses contain a segmented dsRNA genome (11 segments) within a triple layered capsid composed of 3 structural proteins; the VP2 core, the VP6 inner capsid, and the VP7 outer capsid. They cause diarrhea in both human infants and young animals, accounting for ~800,000 deaths in children yearly. Rotaviruses belong to 7 distinct serogroups (A-G) based on antigenic differences in the major viral inner capsid protein, VP6 (Saif and Jiang, 1994). These groups can also be differentiated by their distinct electropherotypes in PAGE and by genetic typing by RT-PCR (Saif and Jiang, 1994). Group C rotaviruses have been detected from diarrheic pigs, adult cows and may be an emerging enteric pathogen in humans, associated with infections in all ages (Saif and Jiang, 1994).

Rotaviruses have a dual serotype specificity based on neutralization determinants present on the 2 outer capsid proteins, the hemagglutinin spike, VP4 (P serotype) and the major outer capsid, VP7 (G serotype) (Estes and Cohen, 1989). In addition, genetic typing of rotavirus P and G types is possible with common types usually showing >89% nucleotide identity. VP4 and VP7 independently induce neutralizing antibodies and genes encoding the P and G determinants segregate independently during co-infections. Thus P and G gene reassortment may account for the origin of new rotavirus strains. For group A rotaviruses, at least 14 G types and 13 P (serotypes) or 20 P [genotypes] are recognized (Estes and Cohen, 1989). Besides serogroup specific determinants on VP6, the VP6 contains distinct subgroup determinants for group

A rotaviruses: subgroup I (most animal strains and human strains with short electropherotypes) and subgroup II (mostly human strains) (Estes & Cohen, 1989).

In addition electropherotyping analysis of all 11 rotavirus genome segments followed by RNA-RNA cross-hybridization allows detection of group A rotavirus genogroups (Nakagomi et al, 1990, 1992). To date 3 major human rotavirus genogroups are recognized: Wa-like, DS-1-like and AU-like. Although thought to be mainly host-specific, recent data suggests that animal rotaviruses may infect humans and vice versa ((Nakagomi et al, 1990, 1992; Gentsch, et al. 1996), suggesting the possibility of zoonotic transmission of rotaviruses. The implications of zoonotic rotavirus infections for the design and efficacy of human rotavirus vaccines is unclear. These topics as well as possible mechanisms involved in rotavirus transmission to new hosts will be discussed.

Zoonotic Rotavirus infections

Early studies to assess evidence for possible interspecies transmission of rotaviruses relied on electropherotyping and subgroup analysis of rotaviruses (Nakagomi et al. 1990, 1992) and detection of human strains that hemagglutinate, a property usually restricted to animal rotaviruses. These studies revealed several human rotavirus strains that were subgroup I but possessed long dsRNA electropherotypes, typical of animal rotaviruses. Further genogroup characterization of these strains by RNA-RNA hybridization identified human strains closely related to feline or canine rotaviruses (AU-1 from Japan and Ro1845 from Israel) (Nakagomi et

al 1990) or bovine rotaviruses (PCP5, MZ58m, PA151, PA169 from Italy and Ro5193 from Israel) (Nakagomi et al, 1992; Gerna et al, 1992; Gollop et al, 1998). At present 3 distinct genogroups of human rotaviruses exist; Wa, DS1 and AU1-like with the P[9],G3 AU1-like human strains divided into subgenogroups more closely related to feline or bovine strains or feline X bovine reassortants (Gollop et al, 1998). Interestingly these strains generally caused sporadic, self-limited, geographically-restricted, mild infections in humans (Gollop et al, 1998) or were most often detected from outpatient clinics (Israeli strains) (Silberstein et al, 1995).

Analysis of P and G serotypes/genotypes revealed further evidence for potential animal to human transmission of rotaviruses. It has been clearly shown in a study of >2700 human rotavirus specimens that the 4 major human rotavirus G types are distributed globally, and excluding mixed infections, the most common types were : P[8],G1 (53%); P[8],G4 (14.3%); P[4],G2 (10.7%) and P[8],G3 (5.4%) (Gentsch et al, 1996). Of particular interest however were the diversity of human rotavirus strains detected by P and G genotyping studies of human rotavirus isolates from developing countries including India, Bangladesh and Brazil. These studies revealed possible transmission of entirely animal P/G types to humans and genetic reassortment between animal and human rotaviruses (Gentsch et al, 1996). Examples of whole virus transmission included detection of P[11],G10 bovine rotavirus-like strains in 34% of specimens from infants with asymptomatic infections in India during 1988-1994 (Das et al, 1993). Interestingly, a recent report further documented that unlike in other

surveys of bovine rotavirus P and G types, in India P[11],G10 and not P[5],G6 was predominant among cow and buffalo calves (Gulati et al, 1999).

A number of examples exist for potential genetic reassortment between animal and human rotaviruses based on G and P typing and genotyping. These include the feline/canine x human strains noted previously from Japan and Israel as well as the high prevalence (70.2%) of bovine-like P types, P[11],G9 strains in asymptomatic neonates in India. Gerna et al (1992) reported the detection of an AU-1 P type, P[9],G6 (bovine-like) rotavirus in children with diarrhea in Italy. Especially noteworthy was the detection of multiple bovine-like G types (G10, 16% and G8, 4%) and mixed G type infections (16%) from Brazilian children with diarrhea (Santos et al, 1998). In addition human P[8]/porcine (G5) reassortants were the third most common (13%) in rotavirus diarrhea cases from Brazil (Gouvea et al, 1995; Gentsch et al, 1996). This finding further coincides with the detection of P[8],G5 strains in pigs in Brazil (Santos et al, 1999). Documentation by these authors of mixed human/animal rotavirus infections in pigs included demonstration of G5 porcine rotaviruses as mixed infections with a P[9],G1 human-like rotavirus. Similarly, Fitzgerald et al (1995) detected a P[11],G6 (lamb) rotavirus as a mixed infection with a P[8],G9 human-like rotavirus. From the results of these studies it appears that infants or young children in close contact with animals (such as in developing countries) are more likely to acquire mixed infections by human and animal rotaviruses potentially leading to human/animal reassortants due to the segmented nature of the rotavirus dsRNA genome.

Of interest was the observation that many of these reassortant rotavirus infections were detected in neonates in hospitals (India) or in children in outpatient clinics (Israel) as asymptomatic infections (Das et al, 1993; Silberstein et al, 1995), although this apparently was not the case in Brazil (Gouvea et al, 1995) or Italy (Gerna et al, 1992). Thus the factors that influence the interspecies transmission and virulence of these reassortant rotaviruses are unknown.

However, another potential predisposing factor for interspecies transmission of rotavirus is likely to be the occurrence of rotavirus infections in highly susceptible immunodeficient or immunocompromised children. In this regard, Beards et al (1992) reported the first detection of a G10 bovine-like rotavirus from a chronically infected immunodeficient child.

It is important in future studies to assess the impact of these newly emerging human/animal reassortant strains on the efficacy of tetravalent human rotavirus vaccines containing the 4 major human rotavirus G-types (G1-4). This will be especially interesting in countries such as India and Brazil where larger numbers of such divergent strains have been recognized. Also enlightening will be the results of monitoring rotavirus strains that may emerge following introduction of rotavirus vaccines. In this regard, studies of rotavirus strains in beef herds in Argentina before and after introduction of bovine rotavirus vaccines should provide useful new data about rotavirus evolution in response to vaccine selective pressure.

Dual infections with rotaviruses: role in interspecies transmission

and adaptation to new hosts

There are few reports of the potential mechanisms for interspecies transmission and adaptation of rotaviruses to new hosts. In studies of group A rotaviruses, Chen et al (1989) showed that gene 4 of the rotavirus variant SA11-4F underwent a functional change after its introduction by reassortment into a new genetic background in the heterologous bovine strain B223 (P[11],G10). Its function was fully expressed only if another SA11-4A gene (VP7 gene) was provided. Thus the resulting reassortants from coinfections may be functionally expressed only with the aid of certain complementary parental genes, requiring the presence of both reassortant and parental strains for disease expression. This may explain why certain reassortants produce only asymptomatic infections following interspecies transmission in the new host.

Studies in our lab of group A/C dual rotavirus infections have also revealed novel findings applicable to the adaptation of heterologous rotaviruses to new host species (Chang et al, 1999). We detected a group C rotavirus genetically and antigenically more similar to porcine than to bovine group C rotaviruses from an adult cow with diarrhea. The cow was coinfecting with a group A rotavirus detectable only in low titer. We examined the pathogenesis of the group C rotavirus in gnotobiotic calves alone or in calves dually infected with virulent group A rotavirus. We found limited or no group C rotavirus shedding, (but group C seroconversion) in the calves inoculated with group C only, suggesting limited viral replication in the intestine. However dual infection of the calves with both the group A and C

rotaviruses led to shedding of the group A and C rotaviruses in all the inoculated calves. Thus we proposed that this group C rotavirus likely originated from a porcine host and that co-infections of calves with group A rotavirus produced synergistic effects in the intestine leading to excretion of the group C rotavirus in feces and its potential transmission and adaptation to cattle upon serial passage.

It is noteworthy that mixed infections with group A and C rotaviruses are common in swine, especially post-weaning, and they may contribute to the severity or transmission of group C

rotaviruses in the diarrhea outbreaks observed in older swine (Kim et al, 1999). Of further significance is the observation that group A rotaviruses were also commonly seen in a number of fecal samples collected from sporadic diarrhea outbreaks in children and adults with group C rotavirus infections (Jiang et al, 1995, and personal communication). Thus we propose that dual infections host-specific and heterologous with rotaviruses may influence disease expression and the adaptation and transmission of rotaviruses to new host species.

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