Viral gastroenteritis

Ulrich Desselberger

Abstract

This article reviews the virology, immunology and epidemiology of the most common viral causes of acute gastroenteritis (rotaviruses, human caliciviruses, astroviruses, enteric adenoviruses). Clinical symptoms range from mild diarrhoea to life-threatening dehydration, and rotavirus disease is a major cause of childhood mortality, mainly in developing countries. The diagnosis, treatment and preventive measures are reviewed. Uncommon viral causes of acute gastroenteritis and viruses causing gastroenteritis in immunodeficient patients are also discussed. Two live attenuated rotavirus vaccines (Rotarix^{RTM}, RotaTeq^{RTM}) have been licensed in >100 countries since 2006 and used in universal mass vaccination (UMV) programmes. In addition, a new rotavirus vaccine was licensed in India in 2015 for UMV. Although rotavirus vaccines are highly effective in industrialized countries, they are less so in low-income countries of sub-Saharan Africa and South-East Asia. Vaccines against human norovirus disease are under development. Major progress has recently been made in basic research on rotaviruses and human caliciviruses.

Keywords Acute viral gastroenteritis; astrovirus; enteric adenovirus; human calicivirus; MRCP; norovirus; rotavirus; rotavirus vaccine; sapovirus

Key points

- Rotaviruses, caliciviruses (noroviruses, sapoviruses), astroviruses and enteric adenoviruses are major causes of acute gastroenteritis in infants and young children worldwide
- Gastroenteritis viruses occur endemically and regularly cause outbreaks or major epidemics
- Since 2006, two live attenuated rotavirus vaccines have been licensed in >100 countries and shown to be effective in reducing severe disease and mortality. Candidate norovirus vaccines are under development
- Recent research developments will enable innovative approaches in basic and translational research into gastroenteritis viruses

Introduction

Acute gastroenteritis with vomiting is easily recognized as a clinical entity but can be caused by very different agents (viruses, bacteria, parasites) or can have a non-infectious cause. Table 1 lists viruses found in the human gut that have been recognized as:

- common causes of diarrhoea and vomiting in humans
- uncommon causes or not a cause of diarrhoea and vomiting in humans
- causes of diarrhoea in immunodeficient individuals.

This article discusses the major groups of viruses that commonly cause gastroenteritis in humans.

The viruses

Rotaviruses,[1] caliciviruses, astroviruses and enteric adenoviruses are the principal virus families involved. Their size, particle and genome structure, classification and epidemiological significance are summarized in Table 2.

Rotaviruses

These are a major cause of infantile gastroenteritis worldwide.

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Structure: rotaviruses comprise an inner core containing a genome of 11 segments of double-stranded RNA and the transcription/replication and capping enzyme complex, a middle layer (inner capsid) consisting of viral protein 6 (VP6), and an outer layer made of VP7 and VP4, the latter protruding as spikes.[1]

Classification: rotaviruses are a genus of the *Sedoreovirinae* subfamily in the *Reoviridae* family, and are routinely classified according to the immunological reactivities and genomic sequences of three of their structural components. Based on cross-reactivities and sequence diversities of VP6, at least nine groups/species (A–H/I) are distinguished.

The surface proteins VP4 and VP7 elicit type-specific neutralizing antibodies. Accordingly, for group A rotaviruses, which cause most human infections, a dual-type classification system has been established, differentiating G types (VP7-specific, 'G' derived from 'glycoprotein') and P types (VP4-specific, 'P' derived from 'protease-sensitive protein'). At present, 27 G types and 35 P types have been described, of which at least 11 G and 11 P types have been found in humans. More recently, genotype classification of the other nine RNA segments has been developed, permitting the detailed study of the evolution and transmission pathways of these viruses.

Replication and pathogenesis: rotaviruses replicate in mature epithelial cells at the tips of the villi in the small intestine. After virus adsorption to sialic acid, human histo-blood group antigens and various co-receptors, viral replication takes place, first in cytoplasmic inclusion bodies termed 'viroplasms', followed by maturation in contact with the endoplasmic reticulum. Mature particles are released from cells by lysis.[1] Rotavirus replication in the gut is rapid and reaches high titres (up to 10^{11} virus particles/ml faeces at the peak of acute diarrhoea) within a short time.

The diarrhoea arises from epithelial necrosis and atrophy, leading to reduced absorption of carbohydrates and an increased osmotic gradient in the gut lumen. There is also a component of hypersecretion contributing to the diarrhoea. The rotavirus non-

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Viruses infecting the human gut

Common causes of diarrhoea and vomiting[a]

- Rotaviruses (11–68%)
- Caliciviruses (noroviruses, sapoviruses) (1–25%)[b]
- Group F adenoviruses (1–10%)
- Astroviruses (1–5%)

Uncommon causes of diarrhoea and vomiting or asymptomatic infection

- Kobuviruses (including Aichivirus)
- Enteroviruses
- Orthoreoviruses
- Adenoviruses (other than group F)
- Toroviruses
- Coronaviruses (including SARS CoV)
- Parvoviruses (including bocavirus)

Causes of diarrhoea in immunodeficient individuals[c]

- HIV
- Cytomegalovirus
- Herpes simplex virus
- Picobirnaviruses
- Adenoviruses types 42–47 (often systemic)

Viruses other than those commonly causing diarrhoea are seen sporadically; on average, viruses represent about one-third of all microbial causes of childhood diarrhoea.
SARS CoV, severe acute respiratory syndrome coronavirus.
[a] Figures in parentheses are detection ranges in various surveys.
[b] Most common cause of outbreaks.
[c] In addition to common causes of diarrhoea and vomiting.

Table 1

structural protein 4 has various functions and acts as a viral enterotoxin.[1]

Immune response: primary rotavirus infection leads to a serotype-specific humoral immune response with initially monotypic protection. During the first 2 years of life, children are repeatedly infected with rotaviruses of various types, resulting in a more complex immune response that seems to provide partial heterotypic protection. Rotavirus-specific secretory antibodies of immunoglobulin A subclass in stool or serum have been identified as an important correlate of protection.[2]

Caliciviruses

Noroviruses (previously termed 'Norwalk-like viruses') and sapoviruses (previously termed 'Sapporo-like viruses') are the two (of five) genera of the *Caliciviridae* family that infect humans. The human noro- and sapoviruses are classified into 5–6 genogroups (I–VI), each group containing 1–19 different genotypes. Noroviruses of different genotypes co-circulate, but genotype II-4 noroviruses predominate worldwide. Genetic recombination among both norovirus and sapovirus strains is not infrequent.

These viruses were first recognized as a cause of human gastroenteritis outbreaks in the 1960s and are now considered the most important cause of non-bacterial gastroenteritis outbreaks and epidemics worldwide. In the UK and elsewhere, calicivirus outbreaks are common in hospital settings, care homes, etc. Human infections with caliciviruses elicit virus-specific immune responses, although these do not seem to provide full protection from subsequent infections.

Astroviruses

Astroviruses are members of the *Astroviridae* family and have a characteristic appearance when viewed by electron microscopy. Within the *Mamastrovirus* genus, two genogroups and a total of 19 genotypes have been differentiated, with human serotypes Ast1–Ast8 being classified as members of genogroup I. Eight different serotypes/genotypes have been distinguished; serotype 1 is most common. Little is known about immunity conveyed after astrovirus infection or the relative cross-protective effect of the immune response on reinfection with heterotypic strains.

Adenoviruses

Enteric adenoviruses of subgroup F (serotypes 40, 41) of the *Adenoviridae* are a less common cause of diarrhoea in infants and small children. They replicate in the cell nucleus and cytoplasm. Some adenovirus proteins inhibit apoptosis; others decrease the expression of host cell proteins, for example, major histocompatibility complex class I antigens on the surface of

Characteristics of viruses that commonly cause acute gastroenteritis in humans

Virus (family)	Size and structure	Genome composition	Classification	Epidemiology
Rotaviruses (*Reoviridae*)	75 nm, triple-layered, wheel-shaped	11 segments of dsRNA totalling 18.5 kb	Groups A–H Within group A subgroups, G and P types Genotypes of all segments	Endemic in children worldwide, winter outbreaks in temperate climates, small epidemics in the elderly
Caliciviruses (*Caliciviridae*)	About 30 nm, surface cup-shaped	ssRNA, 7.7 kb	Two genera infecting humans: noroviruses, sapoviruses	Epidemics in humans of all age groups
Enteric adenoviruses (*Adenoviridae*)	About 70 nm, icosahedral	dsDNA, 36 kb	Group F serotypes 40, 41	Endemic in children
Astroviruses (*Astroviridae*)	About 30 nm, star-like appearance	ssRNA, 6.8 kb	Two genogroups, 19 genotypes	Epidemics in children and adults

ds, double-stranded; ss, single-stranded.

Table 2

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