Viral gastroenteritis

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Acute gastroenteritis and vomiting are easily recognized as a clinical entity, but may be caused by very different agents (viruses, bacteria, parasites), or may have a non-infectious cause.

Figure 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 contribution discusses the major groups of viruses that commonly cause gastroenteritis in humans.

The viruses

Rotaviruses, caliciviruses, enteric adenoviruses and astroviruses are the principal virus groups involved. Their size, particle and genome structure, classification and epidemiological significance are summarized in Figure 2. Their structure on electron microscopy is shown in Figure 3.

Rotaviruses are the major cause of infantile gastroenteritis worldwide.

Structure – rotaviruses comprise an inner core containing a genome of eleven segments of double-stranded RNA and the transcription/replication complex, a middle layer (inner capsid) comprising viral protein 6 (VP6), and an outer layer of VP7 and VP4, the latter protruding as spikes.

Classification – rotaviruses are classified according to the immunological reactivities and genomic sequences of three of their structural components. Cross-reactivities of VP6 distinguish at least seven groups (A–G). Most human infections are caused by group A, which has at least four subgroups (I, II, I + II, non-I, non-II). The surface proteins VP4 and VP7 elicit type-specific neutralizing antibodies. Accordingly, for group A rotaviruses, 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); 15 G types and 23 P types have been described, of which at least 11 G types and 10 P types have been found in humans. Because G and P proteins are encoded by different RNA segments, and rotaviruses of group A are found to reassort readily in doubly infected cells, various combinations of VP4 and VP7 types have been observed in natural human rotavirus isolates.

Replication and pathogenesis – rotaviruses replicate in mature epithelial cells at the tips of the villi of the small intestine. After virus replication, mature particles are released from cells by lysis. Rotavirus replication is rapid and reaches high titres (up to 10^{11} virus particles/ml faeces at the peak of acute diarrhoea) within a short period of time. The diarrhoea arises from epithelial necrosis and atrophy, leading to reduced absorption of carbohydrates and increased osmotic pressure in the gut lumen. Cells emerging from the crypts of the gut epithelium, which exhibit reactive hyperplasia, repair the damage to villous cells. This is accompanied by increased secretion of fluid, which also contributes to the diarrhoea. Recently, a viral non-structural protein (NSP4, encoded by RNA segment 10) was shown to be an enterotoxin (the first viral protein identified to exert this function). Furthermore, a toxic effect of rotavirus infection on the autonomous nervous system of the gut has been described.

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 copro-antibodies of the IgA subclass have been identified as the best correlate of protection.

Viruses infecting the human gut

Common causes of diarrhoea and vomiting[1]

- Rotaviruses (11–68%)
- Caliciviruses (1–13%)[2]
- Group F adenoviruses (1–10%)
- Astroviruses (1–5%)

Uncommon causes or not causes of diarrhoea and vomiting

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

Causes of diarrhoea in immunodeficient individuals[3]

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

Viruses other than those that commonly cause diarrhoea are seen sporadically; on average, viruses represent about one-third of all microbial causes of childhood diarrhoea

[1] Figures in parentheses are detection ranges in various surveys
[2] Most common cause of outbreaks
[3] In addition to common causes of diarrhoea and vomiting

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Characteristics of viruses that commonly cause 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–G Within group A subgroups, G and P types	Endemic in children, winter outbreaks in temperate climates, small epidemics in the elderly
Caliciviruses (Caliciviridae)	About 30 nm, surface cup-shaped	ssRNA, 7.7 kb	Two genera Noroviruses Sapoviruses	Epidemics in 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	Eight serotypes/genotypes	Epidemics in children and adults

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Caliciviruses: noroviruses (previously termed 'Norwalk-like viruses') and sapoviruses (previously termed 'Sapporo-like viruses') are two genera of the Caliciviridae family. They are classified into two or possibly three genogroups containing 16 genotypes. Norovirus genotypes co-circulate, and recombination among norovirus strains has been observed and may be more common than initially anticipated.

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, calicivirus outbreaks are common in hospital settings. Human infection with caliciviruses elicits virus-specific immune responses, though these do not seem to provide full protection from subsequent infections. Indeed, higher pre-existing antibody levels seem to lead to more severe illness on re-infection, which occurs regularly throughout life.

Adenoviruses: enteric adenoviruses of subgroup F (serotypes 40 and 41) are a less common cause of diarrhoea in infants and small children. They replicate in the nucleus and cytoplasm. Some adenovirus proteins inhibit apoptosis and others reduce host cell metabolism, including expression of MHC class I antigens on the surface of infected cells, thereby reducing susceptibility to adenovirus-specific cytotoxic T cells. A serotype-specific humoral immune response provides homotypic protection.

Astroviruses are members of the Astroviridae family and have a pathognomonic appearance on electron microscopy (Figure 3). 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 re-infection with heterotypic strains.

Epidemiology

Rotaviruses: infections occur endemically worldwide, causing about 460,000 deaths each year in children under 2 years, mainly in developing countries. The epidemiology of these infections is complex. There is a strict winter peak in temperate climates, but in tropical and subtropical regions infections occur throughout the year. Transmission is mainly by the faeco-oral route. Nosocomial infections on infant and paediatric wards are difficult to eliminate.

Group A rotaviruses of different G and P types co-circulate in different populations within a geographical location, varying over time. Types G1, G2, G3 and G4 represent more than 90% of co-circulating strains in temperate climates, but other G types are increasing and may even become most prevalent, particularly in tropical and subtropical areas. Non-G1–G4 type viruses are also found in temperate climates (e.g. G9 in the USA and Europe).

Many species of mammal harbour diverse rotaviruses, and increasing data indicate that they may act as reservoirs for human infections. Most human infections are caused by group A rotaviruses; however, group B rotaviruses were established as the cause of acute gastroenteritis outbreaks in children and adults in China in the 1980s, and recently in Calcutta, India and in other South East Asian countries. Group C rotavirus infections are associated with isolated cases and small outbreaks of diarrhoea in humans.

Noroviruses: norovirus infections exhibit a winter peak, and the associated clinical picture has become known as 'winter vomiting disease'. Age-related seroprevalence surveys have shown that many infections with noroviruses occur in the young and are often inapparent. About 50% of children have been infected by the age of 2 years. It is now accepted that the incidence of infection with noroviruses and sapoviruses is largely underestimated. Noroviruses cause outbreaks of acute gastroenteritis, mainly as a result of contamination of food (oysters, green salad) or water. Such outbreaks occur in both children and adults in recreational camps, hospitals, nursing homes, schools and cruise ships.

Astroviruses cause both endemic infections and food-borne outbreaks. Seroprevalence surveys have shown that individuals can become infected by more than one serotype.

Clinical features

Onset of acute viral gastroenteritis is after 1–2 days' incubation, with watery diarrhoea lasting 4–7 days, vomiting and varying dehydration. Fever is not common. As a rule, the duration of diarrhoea with norovirus infection is shorter than that with rotaviruses or enteric adenoviruses. Infection may be accompanied