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Viral Gastroenteritis
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SECTION VI

Other viruses causing gastroenteritis

Introduction

Besides the viruses producing the majority of human viral gastroenteritis (Sections II-V), other viruses infect more rarely, but are sometimes able to cause epidemics. In particular, they cause chronic infection in the immunocompromised.

Toroviruses

Toroviruses comprise a genus of the *Coronaviridae* family (Enjuanes *et al.*, 2000). They are enveloped and possess a genome of single stranded RNA of positive polarity which is approximately 20-25kb in size. The RNA is surrounded by nucleoprotein (N) in helical symmetry. The nucleocapsid has a toroid shape (inspiring the name from *lat.* torus = convex moulding of a column) and is enclosed in an envelope consisting of membrane protein (M) and a lipid bilayer. Inserted in the envelope are the surface proteins S (for *s*pike) and HE (for *h*aemagglutinin-*e*sterase). The HE protein has sequence similarities with corresponding proteins of coronaviruses and influenza C viruses. Toroviruses may have acquired this gene by a recombination event in the past. Replication is special in that mRNA is synthesized from 'core promoters' of a negative stranded RNA template and not by fusion of a common leader sequence with subgenomic transcripts as in the coronaviruses (Snijder and Horzinek, 1995).

Toroviruses are a well-described cause of diarrhoea in calves (BoTV; Breda V) and horses (EqTV, Berne virus) but may also infect sheep, goats and pigs. Humans seem to become infected by a closely related, but distinct virus (HuTV) (Koopmans and Horzinek, 1994; Enjuanes *et al.*, 2000). In cases of human diarrhoea toroviruses have been diagnosed by electron microscopy and EIA (Koopmans *et al.*, 1993). In a recent survey in Canada of 1365 faeces from children with diarrhoea, rotavirus was found in 32%, adenovirus in 4%, torovirus in 3%, Norwalk like viruses in 2%, and astroviruses and Sapporo-like viruses each in less than 1% (Waters *et al.*, 2000). This suggested that toroviruses are not a very frequent, but a consistent cause of diarrhoea in humans (Koopmans *et al.*, 1997; Waters *et al.*, 2000). M Petric has described the epidemiology of toroviruses (Section VI, Chapter 1). As molecular tests become available, the true extent of prevalence and incidence of human TV infections will become apparent.

Picobirnaviruses

Picobirnaviruses are related to, but not recognized yet as, members of the *Birnaviridae* family (Leong *et al.*, 2000). They comprise icosahedral, single shelled, non-enveloped particles which contain 2 segments of double stranded RNA as their genome. These viruses (diameter 60 nm) occur in three known genera: *Aquabirnavirus* (in fish; type species: infectious pancreatic necrosis virus, IPNV), *Avibirnavirus* (in birds; type species: infectious bursal disease virus, IBDV) and *Entomobirnaviruses* (in *Drosophila;* type species: Drosophila X virus (BXV); Leong *et al.*, 2000).

Picobirnaviruses are only 30-40 nm in diameter and have 2 (or sometimes 3) segments of dsRNA as their genome (Leite *et al.,* 1990). They were detected in children with diarrhoea and in several animal species (asymptomatic) (Pereira, 1991; Ludert *et al.*, 1991; Gallimore *et al.*, 1993, 1995). Recently they were found in the faeces of HIV-infected patients with diarrhoea more frequently than in HIV-infected patients without diarrhoea (Grohmann *et al.*, 1993; Giordano *et al.*, 1999), but a virus-specific immune response was not measurable (Grohmann *et al.*, 1993). The viral genome has recently been cloned and sequenced, and reagents derived from this will help to unravel the epidemiology of picorbirnavirus (Rosen *et al.*, 2000). B I Rosen has reviewed aspects of the molecular biology and epidemiology of these viruses (Section VI, Chapter 2).

Enteroviruses

The genus *Enterovirus* of the *Picornaviridae* family contains a large number of species [polioviruses of types 1-3, Coxsackieviruses of groups A (24 types) and B (6 types) and echoviruses (>70 types), Melnick, 1996]. Enteroviruses consist of an almost featureless capsid of 27-30 nm diameter containing 60 protomers, each possessing 3 surface proteins, VP1, VP2, VP3, and, in most viruses, an internal capsid protein, VP4. The capsid encloses a genome of single stranded RNA of positive polarity of 7-8.5 kb length. The RNA has a single open reading frame (ORF) encoding a polyprotein precursor which is co- and post-translationally cleaved in a complex cascade of events into the 3 to 4 structural and a number of non-structural proteins (for details see Racaniello, 2001).

All enteroviruses infect man via the gastrointestinal tract where they have their first site of replication, probably in lymphoid tissues of the pharynx and gut. Usually enteroviruses are excreted in the stool for several weeks after infection but can also be isolated easily from the pharynx. After primary replication viruses spread via blood to other organs (nerve, muscle, fatty tissue) where they replicate further. Most infections are asymptomatic, but enteroviruses can be the cause of meningitis, meningoencephalitis (poliomyelitis), myocarditis, pleurodynia, conjunctivitis and rashes (Melnick, 1996).

In most cases of enterovirus infection there is *no* diarrhoea. However, some diarrhoea outbreaks have been found to be associated with enterovirus infections;

Coxsackievirus A1 and echoviruses of types 4, 11, 14, 18, 19 and 22 have been involved (Townsend *et al.*, 1982; Patel *et al.* 1985; Melnick, 1996).

Recently, echoviruses of types 22 and 23 have been removed from the *Enterovirus* genus and, as they are very different in their sequence from all other *Picornaviridae*, been classified in a separate genus *Parechovirus* (King *et al.*, 2000).

The *Aichi*virus is an at present unassigned species in the *Picornaviridae* family (King *et al.*, 2000), but is proposed as a separate new genus (Yamashita *et al.* 1998). It is icosahedral, and the capsid has only 3 proteins. Virions are stable at pH 3.5. *Aichi*virus grows well in cell culture (BSC-1 and Vero cells) and has been shown to be a consistent cause of human gastroenteritis (Yamashita *et al.*, 1991, 1993). It has also been found as a cause of traveller's diarrhoea (Yamashita *et al.*, 1995). Its genome has recently been cloned and sequenced (Yamashita *et al.*, 1998), and it is hoped that the epidemiology of this virus will be further clarified with the availability of specific molecular reagents. T Yamashita and K Sakae have summarised our present knowledge of Aichivirus in Section VI, Chapter 3.

Human Immunodeficiency Virus (HIV)

HIV, the causative agent of the Acquired Immunodeficiency Syndrome (AIDS), is a member of the *Lentivirus* genus of the *Retroviridae* family. It infects the CD4 subset of lymphocytes overwhelmingly, but also macrophages, using different sets of receptors/coreceptors. Its replication (for details see Freed and Martin, 2001) damages the functions of infected cells before they are destroyed. The infection is symptomless for a long time, but then severe, generalised secondary infections appear (caused by other viruses, bacteria, fungi or protozoa) which are generally lethal.

There is evidence of extensive HIV infection in gut-associated lymphoid tissue (GALT) and also in enterocytes which contribute to the development of chronic diarrhoea in many AIDS patients (Nelson *et al.*, 1988; Heise *et al.*, 1991; Kotler *et al.*, 1991; Rabeneck, 1994).

Herpesviruses

Cytomegalovirus (CMV) and herpes simplex viruses, members of the *Herpesviridae* family, are found as the cause of colitis and oesophagitis, mainly in HIV-infected patients (Levinson and Bennets, 1985; Jacobson and Mills, 1988; Dieterich and Robinson, 1991; Theise *et al.* 1991; Mentec *et al.*, 1994; Cotte *et al.*, 1996). With the application of highly active antiretroviral therapy (HAART) it has become less urgent or indicated to commence and maintain a specific anti-CMV therapy with ganciclovir (Whitcup *et al.*, 1999; Pollok, 2001).

Coronaviruses

Coronavirus is another genus of the *Coronaviridae* family (Enjuanes *et al.*, 2000). The particles are 120-160 nm is diameter, enveloped and possess a genome of linear. positive-sense, single stranded RNA of 27 – 31 kb in size. The genome is surrounded by nucleocapsid protein (N; in helical symmetry) which in turn is contained in an envelope consisting of M protein and a host cell-derived lipid bilayer into which are inserted the surface proteins S (forming spikes), a small membrane protein (E) and the haemagglutinin esterase (HE) protein. Protein is expressed from RNA molecules which are in most cases subgenomic, and all mRNAs carry a leader sequence derived from the 5' end of the genome (for details see Lai and Holmes, 2001).

Coronaviruses infect the respiratory and gastrointestinal tract. They are a recognized cause of common cold in man (McIntosh, 1996). Whilst coronavirus infections are firmly associated with gastroenteritis in animals (e.g. Transmissible gastroenteritis virus (TGEV) of pigs; Kim *et al.*, 2001), their association with gastroenteritis in man has often been claimed, but its significance for human diarrhoeic disease has been controversial and not yet been firmly established (Gerna *et al.*, 1985; Zhang *et al.*, 1994; Siddell and Snijder, 1998; Holmes, 2001).

J Grant has produced a review of the histopathological findings of viral gastrointestinal tract infections, with particular emphasis on the data obtained from the immunocompromised (Section VI, Chapter 4).

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