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Viral Gastroenteritis
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SECTION V

Astroviruses

Introduction

Human astroviruses are members of the *Astroviridae* family. They are non-enveloped viruses possessing a single stranded RNA of positive polarity as their genome (Matsui, 1997; Matsui and Greenberg, 2000). Negatively stained astroviruses appear by EM as spherical particles of 35-40 nm diameter with a characteristic 5-6 pointed star surface configuration which has provided the name for these viruses. Astroviruses are relatively easy to detect in human faeces as they are produced in significant numbers at the onset of illness (by contrast to human caliciviruses, see Section IV), and they have been found to be cultivatable *in vitro* (Lee and Kurtz, 1981; Brinker *et al.*, 2000). This has allowed detailed analysis of the viral replication cycle (Matsui, 1997; Willcocks *et al.*, 1999; Matsui and Greenberg, 2000).

Cryo-electron microscopy and image reconstruction of astroviruses have identified spherical particles of uniform size (330Å diameter) with 30 diploid spikes extending about 50Å from the surface and leading to an external diameter of the particle of approximately 420Å (Yeager and Matsui, 2000; Matsui *et al.*, 2001). These investigations clarified and extended earlier EM data obtained from cell culture grown virus (Risco *et al.*, 1995).

U Geigenmüller *et al.* have reviewed astrovirus replication (Section V, Chapter 1). The genome of astroviruses measures approximately 6.8 kilobases in length, excluding the poly A tract at the 3' end, and encodes 3 open reading frames (ORFs; Jiang *et al.*, 1993; Willcocks *et al.*, 1994) (Fig. 2 in Section V, Chapter 1). ORFs 1A and 1B at the 5' end encode the viral protease and RNA-dependent RNA polymerase, respectively, and ORF2 at the 3' third of the genome encodes a structural protein that is a precursor of the structural proteins of the mature virus (Belliot *et al.*, 1997a; Bass and Qui, 2000). ORFs 1A and 1B are overlapping by 70 nucleotides. This area is highly conserved among human astrovirus serotypes and contains a frame-shifting signal of a "shifty" heptamer (A AAA AAC); downstream there are sequences which form a stem loop structure (Marczinke *et al.*, 1994; Lewis and Matsui 1995, 1996) essential for frameshifting, as part of a replication strategy seen with other viruses (retroviruses, Jacks *et al.*, 1988; coronaviruses, Brierley *et al.*, 1989). I Brierley and M Visakovic have reviewed and updated this topic (Section V, Chapter 2).

A further characteristic of astrovirus replication in cells infected *in vitro* is the production of full length genomic and ORF2-specific subgenomic RNAs; the latter is mainly used for the production of large amounts of structural proteins (Monroe *et al.*,

1993). More detailed investigation of expression products of the ORF1A and deletions thereof identified a protease active domain at the N terminus and a nuclear localization signal domain at the C terminus (Matsui, *et al.*, 2001).

As astroviruses have a genome of single-stranded RNA of positive polarity and as replication *in vitro* after infection with virus particles had been demonstrated, it was tempting to explore the infectivity of naked RNA. This was shown to be possible by transfection of viral RNA of human astrovirus type 1 into BHK cells (which were easier to transfect) and propagation of progeny virus obtained from these cells in Caco-2 cells (Geigenmüller *et al.*, 1997). In the same publication it was shown that infectious RNA could also be transcribed from a full length cDNA clone of human astrovirus serotype 1. This achievement has allowed to identify the functions of sequence regions necessary to produce fully infectious virus (Matsui *et al.*, 2001). A replication and transcription scheme for astroviruses was constructed similar to the one explored in more detail for the life cycles of alphaviruses such as Sindbis virus (Matsui *et al.*, 2001). U Geigenmüller *et al.* have presented recent studies based on the use of infectious cDNA and of mutagenizal derivatives thereof (Section V, Chapter 1). Recently, an infectious cDNA clone has also been obtained from another astrovirus, avian nephritis virus (Imada *et al.*, 2000).

The development of sensitive tests for the presence of astrovirus, e.g. using group reactive monoclonal antibodies (Herrmann *et al.*, 1988) has led to the conclusion that astroviruses are the cause of more cases of childhood diarrhoea than previously assumed. This was confirmed by the development of RT-PCR detection assays which also proved not infrequent asymptomatic shedding of astroviruses in older children (Jonassen *et al.*, 1995; Mitchell *et al.*, 1995). Astroviruses have also been identified as the cause of major outbreaks of diarrhoea and vomiting (e.g. Oishi *et al.*, 1994).

Different serotypes of human astrovirus have been defined on the basis of immune electron microscopy, neutralization tests and type-specific EIAs (Lee and Kurtz, 1994; Noel *et al.*, 1995). So far 8 different serotypes have been identified, and it has been shown that differences in the sequences of RT-PCR products from a region within ORF2 correlated precisely with antigenic types determined by type-specific EIA (Noel *et al.*, 1995).

The study of astrovirus serotypes in various populations has demonstrated that type 1 was the most commonly detected, whilst types 6-8 were rarely found and types 2-5 at intermediate frequencies (Lee and Kurtz, 1994; Noel and Cubitt, 1994; Noel *et al.*, 1995). Age-stratified seroprevalence studies of neutralising antibodies to astroviruses types 1-7 in humans in the Netherlands showed that subjects had been infected by several serotypes and that the antibody prevalence against several serotypes exceeded their relative isolation rate, suggesting that many infections are of milder clinical consequence or asymptomatic (Koopmans *et al.*, 1998). Human astroviruses were found to a very high percentage in shellfish and mussel (Le Guyader *et al.*, 2000).

Cocirculation of multiple astrovirus serotypes was shown by several groups in different locations (Noël *et al.*, 1995; Cunliffe *et al.*, 1998; Naficy *et al.*, 1999; Mustafa *et al.*, 2000; Monroe *et al.*, 2001), and the different types are seen to cluster in 2 genogroups (A: types 1-5; B: types 6, 7; Belliot *et al.*, 1997b). The assignment of type 8 to

a genogroup seems to depend on the genome area used for evaluation and raised the possibility that RNA recombination might have occurred in astroviruses. (Belliot *et al.*, 1997b; Monroe *et al.*, 2001). S Monroe has described recent aspects of the molecular epidemiology of astroviruses (Section V, Chapter 3).

Progress in diagnosis of astrovirus infections with molecular techniques has established them as a not uncommon cause of acute gastroenteritis in infants and young children. Although enteric astrovirus strains have been isolated from animals, e.g. from turkeys (Koci *et al.*, 2000), there are so far no firm data supporting the possibility that human astroviruses are derived from an animal reservoir or that animal astroviruses infect humans on a larger scale.

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