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Review

# Novel human astroviruses: Novel human diseases?

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ABSTRACT

Astroviruses are small, non-enveloped, single-stranded positive RNA viruses that belong to the *Astroviridae* family. While classical human astroviruses (HAstV) are a well-recognized cause of acute non-bacterial diarrhea among young children worldwide, novel astroviruses, named HAstV-MLB and HAstV-VA/HMO, have been identified recently in humans by molecular assays. They are phylogenetically more related to animal astroviruses than to classical human astroviruses, thus suggesting cross-species transmission. Serological studies demonstrated a surprisingly high seroprevalence in certain populations and highlighted a high infection rate in the early years of life. Although their pathogenic role has not yet been clearly determined, novel astrovirus RNA sequences have been identified in different biological specimens of symptomatic patients, including the feces, plasma, cerebrospinal fluid, and brain biopsies. Thus, there is evidence that they could contribute not only to digestive tract infection, but also to unexpected clinical syndromes, notably encephalitis and meningitis. Severe infections affect mainly immunocompromised patients. These findings indicate that novel astroviruses should be considered in the differential diagnosis of immunocompromised patients with meningitis or encephalitis of unknown origin.

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## 1. Introduction

Human astrovirus (HAstV) was first described in 1975 [1]. Since then, astrovirus infections are a well-recognized cause of gastroenteritis worldwide and affect mainly young children under 2 years. They are responsible for up to 10% of non-bacterial gastroenteritis [2,3] and constitute the third most common viral agent of acute diarrhea after rotavirus and norovirus [4]. Recently, the screening of human feces by molecular assays revealed the existence of novel astroviruses, HAstV-VA/HMO and HAstV-MLB, that are phylogenetically markedly distant from the classical HAstV [5–11]. Little is known about these novel astroviruses in terms of epidemiology, clinical disease, and pathogenesis, but according to the increasing number of reports, we can now confirm that they are circulating in several parts of the world. In addition, there is growing evidence that they are associated with clinical syndromes, including unexpected central nervous system (CNS) infections in vulnerable populations. The aim of this study is to describe the epidemiology and clinical presentation associated with astrovirus infections in humans.

## 2. Classical human astroviruses

Classical HAstV are members of the *Astroviridae* family and are composed of eight distinct serotypes. Serotype 1 is the most prevalent and infection seems to occur within the early years of life, with a seroprevalence of 90–100% by age 5 [12,13], whereas seroprevalence of serotypes 6 and 7 is much lower (16% and 10%, respectively) [2,12]. Serotype 3 has been associated with persistent gastroenteritis [14]. HAstV is responsible both for sporadic cases and epidemics, as well as nosocomial infections [15]. The clinical manifestation is usually mild, short and self-limited, lasting for 2–4 days, typically consisting of watery diarrhea, but also vomiting, fever, abdominal pain, anorexia, and headache [16]. As for many viral infections, asymptomatic carriage has been described in 2% of children under 5 years of age [3].

In adults, astroviruses primarily affect older and immunocompromised patients. In the latter group, astroviruses can cause more severe digestive symptoms and of longer duration, as well as disseminated infections with extra-digestive infections [15,17,18].

## 3. Virus and pathogenesis

Astrovirus is a non-enveloped, positive-sense single-stranded RNA virus of 28–41 nm in diameter that shares conformational similarities with the hepatitis E virus [19]. The RNA genome is 6.4–7.7 kb in size, depending on subtype and species, and contains a covalently-linked VPg protein at the 5′ end, which likely contributes to the virus infectivity [20]. The astrovirus genome consists of three open-reading frames (ORF), namely ORF1a, ORF1b and ORF2. Translation of these genes results in three polyproteins, the capsid protein VP90 and the non-structural proteins nsp1a and nsp1ab, that after several cleavages by host caspases, result in the capsid proteins, the viral serine protease, the RNA-dependent RNA polymerase and other non-structural proteins [21]. Replication of viral particles on cell culture is difficult and different cell lines may be required according to the astrovirus subtype [16,22]. This suggests that there may be different, yet unrecognized, receptors for cell entry and thus distinct tropism. Of note, a system of reverse-genetics has been described [23]. Caco2 cells are classically used and recently a clathrin-dependent pathway for cell entry has been identified [24]. The addition of trypsin, permitting a conformational change of the capsid proteins and maturation to infectious virion, enhances virus infectivity, although the optimal concentration may differ according to the experimental setting.

Astrovirus pathogenesis has not been fully elucidated. Controversies between *in vitro* studies and animal models exist concerning astrovirus infection-induced cell death [25,26]. Histopathological examination reveals little inflammatory reaction at the site of virus replication, mostly the jejunum [27,28]. Replication occurs on the apical two-thirds on the intestinal villi, but has also been reported in macrophages present in the lamina propria [28]. The mechanism of astrovirus-induced diarrhea is not clearly established and cell apoptosis [25], decreasing maltase activity [29], or an increase in the epithelial barrier permeability [30] have all been suggested to play a role.

## 4. Taxonomy

The *Astroviridae* family is divided into two genera, *Mamastrovirus* and *Avastrovirus*. Mamastroviruses infect a wide variety of mammals, while avastroviruses infect poultry, mainly chickens, ducks, and turkeys. Following the discovery of novel astrovirus variants both in animals and humans, the taxonomy of the *Astroviridae* family was revised in 2010 [2]. Indeed, according to the observation that one single host could be infected by several astrovirus species and inversely, therefore typical characteristics of the genome are now considered to define astrovirus species. Although not officially accepted by the International Committee on Taxonomy of Viruses, the term “genotype species” has been proposed [2].

Strains belonging to the same astrovirus species share >65–70% identity in their capsid protein level [2], while a distinct subtype within the same species is defined as sharing <93–95% of nucleotide identity with a reference strain, or >0.05 distance by phylogenetic analysis, based on the capsid gene sequence [2,16]. Novel astroviruses, such as HAstV HMO or MLB, share approximately 40% nucleotide capsid sequence identity and 45% full-length sequence identity with classical HAstV serotype 1 [31]. The spectrum of animals that are infected by astroviruses is constantly expanding [32,33] and novel subtypes and new species are regularly identified [34–36]. This can be attributed to novel highly sensitive diagnostic tools, but could also be explained by the constant evolution and genetic diversification of these viruses.

To date, four distinct astrovirus species have been identified in humans: *MAstV 1, MAstV 6, MAstV 8 and MAstV 9.* Phylogenetic tree of human astroviruses is shown in Fig. 1.We will now focus on the so-called “novel” astroviruses, namely *MAstV 6* (astrovirus MLB1-3), *MAstV 8* (astrovirus VA2 – also named HMO-A, VA4 and VA5), and *MAstV 9* (astrovirus VA1 and VA3 – also named HMO-C and HMO-B respectively).

### 4.1. Mamastrovirus 6

The representative strain of *MAstV6*, astrovirus MLB1, was identified in the stool sample of a 3-year-old child with diarrhea in Melbourne who had undergone a liver transplant previously [6]. The stool samples were collected in 1999, supporting the hypothesis that novel astroviruses have been circulating in humans for decades. The second subtype, MLB2, shows 71.8% nucleotide sequence identity with MLB1 based on the capsid sequence. In a cohort of 176 children with fever of undetermined origin at St Louis Children’s Hospital (St Louis, Missouri), astrovirus MLB2 was identified in the plasma and nasopharyngeal swab of a child (prevalence, 0.6%) [37,38]. Astrovirus MLB3 with 72.3% nucleotide sequence identity with MLB1 and 80.2% with MLB2 was identified in children with and without diarrhea in India, Kenya and The Gambia [9,10]. A seroprevalence study of 395 healthy volunteers for an influenza vaccine trial ranging from 2 months to 95 years in USA, astrovirus MLB1 antibody was detected in 342 subjects (86.6%), with the highest seroprevalence in the 7–17 years age group (100%) [39].

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