Rafidain Journal of Science
https://rsci.mosuljournals.com
Vol. 33, No.2, pp. 102-113, 2024

Review Article

Human Astrovirus and Associated with Gastroenteritis and Encephalitis

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p-ISSN: 1608-9391
e -ISSN: 2664-2786

Article information

Received: 1/9/2023
Revised: 1/11/2023
Accepted: 10/11/2023

DOI: 10.33899/rjs.2024.183430

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ABSTRACT

One of the most important causes of viral acute gastroenteritis in children has been thought to be human astroviruses. Yet, recently identified highly divergent human astroviruses that cause persistent diarrhea and extra-intestinal infections have been shown to infect people. The intestinal epithelium's ability to operate as a barrier is affected, and the tips of the microvilli are blunted.

The isolation of astrovirus VA1/HMO-C (VA1; mamastrovirus 9) and classic human astrovirus 4 (HAstV4; mamastrovirus 1) from cases of human encephalitis has been documented in reports of fatal cases of meningitis and encephalitis. It is crucial to assess the ability of these two astrovirus genotypes to infect and spread by utilizing human primary neurons, human primary astrocytes, and other immortalized human nervous system cells. The disease range has been expanded, particularly among those with compromised immune systems. The occurrence of zoonotic transmission of Astroviruses between humans and animals has not been demonstrated, although it is probable because to the genetic similarities between many human and animal viruses.

Keywords: Enzyme-linked immunosorbent assay, encephalitis, gastroenteritis, Human Astrovirus, Polymerase Chain Reaction .

INTRODUCTION

Human astroviruses (HAstVs) are a kind of virus that belongs to the Astroviridae circle of relatives. They are tiny, superb-experience single-stranded RNA viruses that lack an envelope. The HAstV virus is a not unusual purpose of viral gastroenteritis globally, and in step with the World Health Organization (WHO), it's miles one of the primary reasons of diarrheal infection (Banyai *et al.*, 2018).

Outbreaks of gastroenteritis arise in kindergartens, colleges and different houses. The aforementioned functions are associated with the maximum frequent HAstV infections, which commonly manifest as moderate signs. As well as, infections because of rotavirus, norovirus, and adenovirus (Pijnacker *et al.*, 2019).

Astroviruses, especially HAstV-VA/HMOu and HAstV-MLBt, have the potential to reason extensive neurological disease in vulnerable populations, inclusive of children, the elderly, or the immunocompromised diseases (Cordey *et al.*, 2016).

Three open reading frames (ORFs) may be located in the genome of HAstVs, ORF1a, ORF1b, and ORF2. The ORF1a and ORF1b genes encode NSPs that play a role in RNA transcription and replication, while ORF2 encodes capsid proteins (Wu *et al.*, 2020).

According to the International Committee on Virus Classification (ICTV) (Bosch *et al.*, 2014), there are 3 forms of HAstVs: traditional HastVs (mammalian astrovirus 1, MAstV 1), HAstV-MLB (MAstV 6), and HAstV -VA/HMOu (MAstV). Eight and (MAstV 9). The maximum not unusual HAstV traces (HAstV-1–HAstV-eight) encompass eight genotypes, every with a particular serotype. Twenty households or subtypes ranging from HAstV-1 to HAstV-6 had been identified. These encompass HAstV-1a to 1f, HAstV-2a to 2nd, HAstV-3a and 3b, HAstV-4a to 4c, HAstV-5a to 5c, and HAstV-6a and 6b. A novel HAstV-three pressures, HAstV-3c, changed into described by Medici *et al.* (2015) and the author. HAstVs are transmitted through direct contact with infected folks and gadgets, observed via consumption of inflamed meals or liquids. The clinical manifestations of HAstV infection are excessive stools lasting about 3 days, observed by means of repeated bloody stools lasting up to 10 days, accompanied by way of symptoms together with cough, fever and abdominal pain to (Bosch *et al.*, 2014).

Astroviruses have been shown to disrupt the integrity of intestinal tight junctions, increasing the permeability of epithelial cells. Disruption of intestinal integrity leads to loss of water and nutrients, resulting in loss of ions, solutes, and fluid migrates between spaces, ultimately leading to acne because it forms the main barrier between the lumen and the basement membrane. In addition, cases of gastrointestinal astrovirus have been documented in human and animal populations (Blomström *et al*., 2010).

Two astrovirus strains, Melbourne (MLB) and Virginia/ Human-Mink-Ovine-like (VA/HMO), have recently been found as phylogenetically distinct from the original HastV, the newly identified HAstVs are accountable for infections affecting the central nervous system, particularly in youngsters with weakened immune systems who experience gastrointestinal symptoms including meningitis and encephalitis. Too far, there exists a solitary instance in which the classical HAstV genotype 4 has been related to infections affecting the vital anxious device in an Austrian hospitalized new child identified with extreme mixed immunodeficiency (SCIDi). Recombination is a common prevalence in several families of RNA viruses. According to Aguado *et al*. (2018), RNA viruses have advanced a mechanism to counteract the host's antiviral RNA interference through recombination, have confirmed that recombination can also take place in ordinary HAstV strains, thereby documenting a number of the early instances of astrovirus recombination's (Aguado *et al*. 2018).

The recombinant HAstV pressure become examined for the presence of the ORF1b-ORF2 overlap region from HAstV-3 and the ORF2 element from HAstV-five, which shows a recombination event. The recent identity of recombination evidence among traces of HAstV-MLB3 and HAstV-MLB1 or -MLB2 has been reported with the aid of Hata *et al.* (2018).

History and Classification

When the scientist used electron microscopy (EM) to find out 28–30 nm particles within the faces of children who had minor diarrhea and vomiting. The subsequent year, and quot; astroviruses and quot; (AstV) have been named for the tiny, globular viruses that Madeley and Cosgrove located in the feces of hospitalized toddlers with gastroenteritis. These particles have been categorized as and quot; small round viruses and quot; (SRVsi) together with different viruses that had a smooth complete edge, as opposed to the and quot; small round structured viruses and quot; (SRSVs), which blanketed particles with a difficult, hairy, or irregular part, like caliciviruses. The family Astroviridae turned into proposed as a novel subfamily of superb-feel single-stranded RNA (ssRNA) viruses, awesome from the households Picornaviridae and Caliciviridae. This was made feasible with the aid of AstV's polyprotein processing and genomic and subgenomic structure. (Xing *et al*., 2010).

The Astroviridae family was formally recognized by the international committee for the taxonomy of viruses (ICTV) in its sixth report dated 1995. The taxonomy of the Astroviridae family, which at first only had one genus of Astrovirus was based on the morphology of the virus. Later on, however, the ICTV suggested a new nomenclature and classification scheme depending on the host of origin. Two genera, genus Mamastrovirus (MastVs) and genus Avastrovirus (AAstVs), which featured viruses that attacked mammals and avian species, respectively, were created from the family. Based on the kind of animal that served as the host and the virus's initial source, asteroids were further separated into viral species within genera. The genus Avastrovirus contains three species (Chicken, Duck, and Turkey astroviruses), whereas the genus Mamastrovirus contains six species (Bovine, Feline, Human, Mink, Ovine, and Porcine astroviruses). Since the publication of the Ninth ICTV Report, this classification has not changed. (Bosch *et al*., 2014).

Kingdom: Orthornavirae
Phylum: Pisuviricota
Class: Stelpaviricetes
Order: Stellavirales
Family: Astroviridae
Genus: Astrovirus
Species: Astrovirus

Virion Structure

The AstV virion is an icosahedral, unenveloped particle with a smooth border. Certain virions (about 10%) have a characteristic five- or six-pointed star on their surface Fig. (1). The about 90 kDa VP90 precursor protein is used to construct particles. Cellular caspases then continue the processing to create the VP70uprotein, which lacks an acidic C-terminalodomain, From the trypsin-cleaved 70-kDa protein, which is an immature particle, trypsin cleavages are required to form Highly infectious particles (VP34, VP27/29, and VP25/26) having capsid proteins of 32 to 34, 27 to 29, and 25 to 26 kDa,VP34 is produced from the polyprotein's highly conserved N-terminal region and aids in the formation of the capsid shell, in contrast to VP27/29 and VP25/26, which are both derived from the variable C-terminal domain with a unique N-terminus (Xing *et al*.,2010).

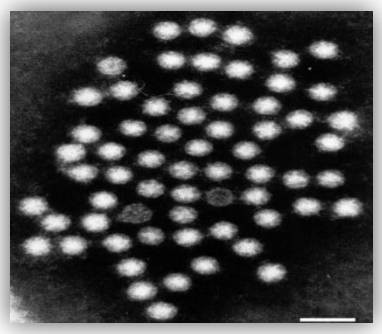

Fig. 1: Transmission immunoelectron microscopy images of human Astrovirus particles in feces stained negatively for phosphotungstic acid. Bar, 50 nm (Bosch *et al*., 2014).

According to transmission EM research, the size of viruses formed in cell monolayers is greater, and they have exterior spikes with a diameter of 41 nm, and lack the recognizable star-like appearance of viruses shed in feces, which are smaller and have an external diameter of 28 to 30 nm.

The AstV spike's crystal structure without its C-terminaloend has been determined. Surprisingly, the design, size, and appearance of the AstV spike strongly resemble those of the hepatitis E virus, the single additional individual of the freshly identified Hepeviridae family (Xing *et al*.,2010). The composition of the AstV protein, which is essential for determining virus specific infectivity, has not changed despite advancements in our understanding of virion structure Fig. (2). (Méndez *et al*., 2014).

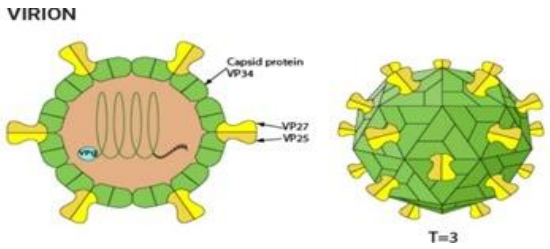

Fig. 2: Structure of Astrovirus (Wohlgemuth *et al*., 2019).

Genome Organization

Astroviruses consist of ssRNA genomes with an estimated length of 6 to 8 kb (Méndez *et al*., 2013). This viral genome consists of three open reading frames, two untranslated regions at both ends, and ORFs. Following Cortez *et al.* (2017) and Méndez *et al.* (2014), the first two ORFs, namely ORF1a and ORF1b, are situated close to the 5′ terminus of this RNA molecule. They encode nonstructural proteins needed for viral replication, which is essential for astrovirus generation, other parts are made up of structural proteins. Some of the replicative proteins include RNA-dependent RNA polymerase, serine protease encoded by the virus, and Viral Protein genome-related (VPg) (RdRp). A frameshift mechanism is used to translate ORF1b (Wohlgemuth *et al*., 2019).

The final open reading frame, orf2, encodes the structural protein Fig. (3). According to Wohlgemuth *et al*. (2019), it is believed that the ORF2 of the astrovirus is encoded on a subgenomic RNA, based on the similarities in the structure and organization of the astrovirus and alphavirus genomes. Indeed, cells infected with astroviruses exhibit two distinct types of +ssRNA: a complete genomic RNA and a subgenomic (sg) RNA measuring approximately 2.4 kilobases.

Negative-sense full-length RNA is produced using full-length genomic RNA and acts as a template for both sgRNA and genomic RNA transcription (Méndez *et al.*, 2014). This is predicated on the idea that astroviruses copy and translate their RNA similarly to how alphaviruses do.

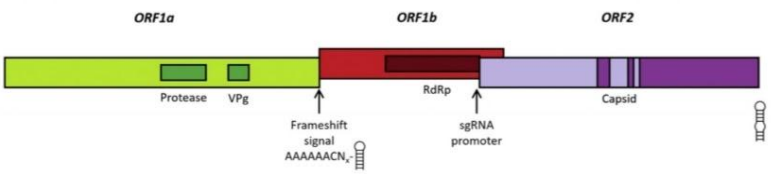

Fig. 3: Genomic architecture of viruses. Inset boxes serve as markers for specific protein coding regions whose identities are known. The darker regions in ORF2 represent the hypervariable region of the capsid protein. A frameshift signal made up of a slippery sequence and a hairpin exists between ORF1a and ORF1b. The genome's 3′ end has a highly conserved hairpin. (Méndez *et al*., 2014).

Symptoms

One of the many microorganisms that can cause gastroenteritis in humans are astroviruses. Diarrhea is the primary astrovirus symptom. The diarrhea brought on by an astrovirus is typically moderate compared to the diarrhea brought on by rotavirus and norovirus (Jeong *et al*., 2012).

While moderate diarrhea is the primary symptom caused by astroviruses, a sick individual may also experience other typical gastroenteritis symptoms, such as:

- Vomiting
- Nausea
- Stomach soreness
- loss of Appetite
- Body pains
- Fever.

Symptoms of Astrovirus infections:

Infants, young children, the elderly, and individuals with compromised immune systems are particularly susceptible to dehydration (such as those undergoing cancer treatment or HIV-positive individuals). (Bosch *et al.,* 2014).

The majority of healthy individuals with a functioning immune system recover from an astrovirus infection in a few days. Because they are otherwise asymptomatic, they may occasionally not even be aware they have an astrovirus infection (without symptoms) A "carrier" is a person who is infected but does not exhibit symptoms; they are nonetheless capable of transmitting the virus to others (Vu *et al*., 2019).

Pathogenesis

Human astroviruses (HAstVs) are thought to be the cause of 0.5–15% of diarrheal outbreaks and 20% of occasional episodes of non-bacterial diarrhea. They primarily afflict infants, the elderly, and people with compromised immune systems, The fecal-oral pathway is the most likely means of astrovirus transmission, Watery diarrhea is the most common indication of infection and normally lasts for two to four days. Vomiting, headaches, fever, abdominal pain, and anorexia are less common (Mitchell *et al*., 1999).

Compared to rotavirus or norovirus infections, astrovirus infections are less likely to cause vomiting, and they take a little longer to incubate. In newborns, two separate investigations HAstV infection and necrotizing enterocolitis have been linked (Chappé *et al*., 2012).

Astrovirus has been found in epithelial cells in the lower section of villi in duodenal biopsies in people, The majority of the time, gastroenteritis caused by an astrovirus is a minor, self-limiting condition. Infants with HAstV infection have been noted to experience intussusception, a type of intestinal blockage in which a portion of the colon prolapses into a more distal portion (Al-Noamy, 2020).

Moreover, severe cases of astrovirus gastroenteritis have been documented (Naflcy *et al*., 2000), and immunocompromised people frequently experience persistent diarrhea (Gallimore *et al*., 2005). Nonetheless, there is proof that both children and adults can have asymptomatic HAstV infections, sharpening of the microvilli at the tips and changes to the intestinal epithelium's barrier function are two hallmarks of astroviral infection. In addition to

destroying the intestinal epithelia and causing malabsorption, astroviruses can also cause diarrhea by altering ion channels, intestinal disaccharidase activity, or intestinal epithelial barrier permeability (Meliopoulos and Schultz-Cherry, 2012).

In addition to inflicting gastroenteritis in younger kids and the aged, HAstVs had been observed to be related to encephalitis and meningitis in people with weakened immune structures (Vu *et al*., 2016). One unique genotype, VA1/HMO-C, has been linked to five instances of encephalitis (Lum *et al*., 2016), in addition to the MLB institution, immunocompromised sufferers are specifically liable to developing encephalitis and meningitis from HAstVs, further to experiencing gastroenteritis (Vu *et al*., 2016). The genotype VA1/HMO-C has been especially associated with 5 instances of encephalitis to date, as well as the MLB organization (Lum *et al*., 2016).

Still, the absolutely special forms of HAstVs called MLB and VA/HMO, which were very recently located, show that additionally they harm tissues and organs beyond the gastrointestinal tract; accordingly, these viruses are liable for CNS contamination in a few sufferers, immunocompromised sufferers with acute encephalitis have additionally been determined to be inflamed with HAstV-VA1/HMO-Ci. In well known, patients who're immunosuppressed are best inflamed by using the maximum currently defined HAstVs within the CNS (Cordey *et al*., 2016).

Based on the existing statistics, the diagnostic system for acute central anxious gadget (CNS) infection as a result of astrovirus more often than not is based on medical observations, precise identification of astrovirus in the cerebrospinal fluid (CSF), predominantly finished thru next-technology sequencing (NGS)-based totally diagnostic techniques, and the exclusion of alternative aetiologies of encephalitis, together with the one. Prior studies performed on people with weakened immune systems who're inflamed with HAstV-MLB or VA strains has indicated that the infection is more likely to arise within the intestines, accompanied through the unfold of the virus all through the mind. Additionally, previous research has documented the localization of HAstV-VA1 in astrocytes and neurons (Maximova *et al*., 2023).

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Diagnosis

A physical examination, a review of your medical history, and different blood and stool tests are typically used to identify astrovirus. If the symptoms are modest, your doctor can decide to treat you presumptively after reviewing your symptoms and risk factors (Pérot *et al*., 2017).

In some circumstances, your physician may prescribe a series of tests to pinpoint the precise cause of diarrhea, particularly if the signs and symptoms are severe or there is a localized epidemic of the illness. The tests could consist of:

• Stool culture to visually and chemically examine a stool sample for astrovirus.

• The enzyme-linked immunosorbent assay (ELISA), a blood examination that looks for immunological proteins called antibodies that the body makes in response to contagious germs. Tests using the polymerase chain reaction (PCR) can find astrovirus RNA in blood. (Li *et al*., 2023; Xu *et al*., 2023).

HAstV Replicative Cycle

The parts that follow and discuss how HAstVs reproduce mainly discuss the so-called "classic" HAstVs. There are several similarities between the HAstV replication cycle and the Caliciviridae family's replication cycles Fig. (4). During cell entry and uncoating, the two significant nonstructural polyproteins, nsP1a (102 kDa) and nsP1a1b (160 kDa), are translated from the VPg-linked genomic RNA. RFS between ORF1a and ORF1b enables expression of the nonstructural polyprotein nsP1a1b. (Marczinke *et al*., 1994).

In replication complexes that are closely clustered around intracellular membranes, the specialized nonstructural proteins necessary for genome replication are deconstructed from these polyproteins. As a result of this procedure, genomic and subgenomic RNAs are produced, resulting

in large yields of structural proteins. The maturation and discharge of virions from the cell come after encapsidation. Although it is generally known that animal calicivirus virions contain genomic and subgenomic RNAs, it is still uncertain if a similar mechanism occurs in AstVs (Neill, 2002).

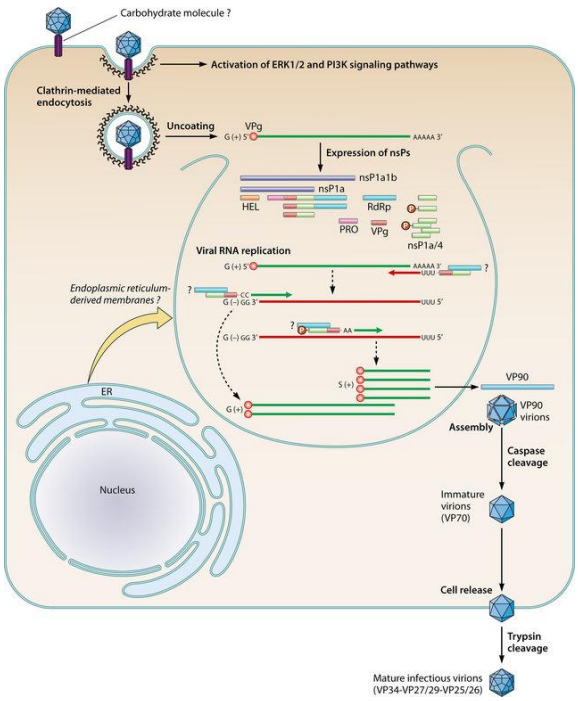

Fig. 4: Astroviruses in humans replicating (Bosch *et al*., 2014).

Capsid Receptor Binding and Entry

Among the virus's unanswered questions is how it takes control of the host cell's receptors and initiates its way inside. Besides guarding the viral DNA, AstV capsid has to collaborate with the host cell during the process of entry. The characteristics of the spike domain represent it as a possible binding domain, according to earlier investigations done by various researchers about prospective receptors, an unconfirmed interaction suggests that the HAstV-8 spike protein structure could have charged residues forming binding sites with di/trisaccharide moieties as a recurring feature, receptor interaction has led to numerous identified cellular entry and absorption mechanisms. According to RNA interference studies performed on Caco-2 cells, the initial uptake appears to be through clathrin-mediated endocytosis (Méndez *et al*., 2014).

The enzyme protein disulfide isomerase A4 (PDIA4) was found to play a role in the degradation of the human astrovirus during its entry into the cell, through thiol-disulfide exchange and unfolded protein response (Aguilar-Hernández *et al*., 2021; Galligan and Petersen, 2021). Notably, different astrovirus strains displayed varying interactions with PDIA4. For instance, HAstV-1 and HAstV-8 spike proteins were able to bind with PDIA4, leading to interference when PDIA4 was inhibited; however, there was no such association observed for HAstV-2. This suggests that the alterations of HAstV-1 to 8 strains' sequence and structure could alter how the virus interacts with the receptors, gains entry into the cell, and ultimately releases its RNA. These differences may then be amplified in more divergent VA and MLB strains (Ykema and Tao, 2021).

Transmission

The evolution of RNA viruses has been drastically stimulated via the transmission patterns observed among various animals. Influenza and ebolaviruses are transmitted from animals to humans and are taken into consideration zoonotic. However, the transmission among unique species is uncommon, even though numerous viruses have a records of sharing hosts (Zhang *et al*., 2018). Nevertheless, interspecies interactions can be altered through environmental and socioeconomic variables, which can also cause heightened publicity to zoonotic viruses (Redding *et al*., 2016). Astroviruses show off more environmental resilience compared to different enteric viruses due to their absence of an outer lipid membrane, enabling them to endure out of doors a host organism for extended intervals (Mendenhall *et al*., 2015). As a result, astroviruses are frequently encountered in water sources. Transmission through the fecal-oral direction has been documented in preceding studies (Méndez *et al*., 2014).

Research performed by means of Gyawali *et al.* (2018) and Boujon *et al*. (2017) has proven the presence of astroviruses in each animal and human sewage and purified wastewater. Boujon *et al*. (2017) have recognized a capability hazard of infection associated with the ingestion of contaminated drinks or meals items, consisting of shellfish (Le Guyader *et al*., 2000) and unwashed culmination and greens (Bosch *et al*., 2014). Not simply infants, however additionally adults can shed asymptomatic viruses, which include HAstV infections. Asymptomatic meals handlers are usually greater susceptible to foodborne outbreaks in comparison to symptomatic ones, regardless of whether or not they are resulting from an endemic or not now (Todd *et al*., 2007).

According to the World Health Organization children residing in developing nations show off heightened vulnerability to gastroenteritis due to elements inclusive of the presence of infected water, insufficient sanitation facilities, and substandard hygiene practices. A surveillance evaluation performed in France has revealed that endemic aquatic astrovirus is a huge contributor to digestive ailments (Gofti-Laroche *et al*., 2003).

According to Gallimore *et al*. (2005) and Cubitt *et al.* (1999), femites have a good-sized role within the transmission of HAstV through automobiles in institutional settings such as hospitals, daycare centres, and geriatric centres. HAstV has the capacity to last on inanimate surfaces for an prolonged length and with a sufficiently increased viral load, as a result providing a large health threat to inclined hosts, classic HAstVs have a minimal survival period of two days on non-porous surfaces inclusive of rest room tiles, while they can persist for at the least one week on porous surfaces like bathroom paper or bed linen, novel HAstVs have been commonly detected in sewage samples, however their prevalence may be somewhat lower than that of classic HastV. Citations: Lizasoain *et al*. (2015).

Control and Prevention

Effective control of virus spread plays a key role in curbing HAstV infections. One of the most effective means to prevent transmission through personal contacts is to always keep hands clean by frequent use of soap and water, particularly after using the toilet and changing diapers, and also before eating or preparing food. Moreover, it is highly recommended that potential fomites should be disinfected. Alcohol (90%) has been found effective for cleaning non-porous surfaces and hands. Although bleach use is encouraged, there are currently no data on novel HAstV survival and inactivation strategies (Vu *et al*., 2017). The greatest method for preventing foodborne and waterborne astrovirus epidemics is the detection and inactivation of astrovirus in food and water. Although there are various ways to find and measure HAstVs, they are not routinely evaluated in matrices of at-risk water and food (Vu *et al*., 2017). In order to effectively inactivate the classic HAstV, drinking water must be disinfected for two hours with 1 mg/mL of free chlorine. Recently, two subunit vaccine candidates that successfully induce a positive IgG response in mice have been revealed (Xia *et al*., 2016). With HAstV, a similar approach might be intended. The proteins from the norovirus spike P protein, the rotavirus VP8 protein, and the avian astrovirus spike P protein have been combined to form these possibilities. Despite the fact that case reports have mentioned

them, the effectiveness of corticosteroids, ribavirin, and PEG-interferon in treating new astrovirus brain infection has not been well established (Naccache *et al*., 2015).

CONCLUSION

Human astroviruses are highly prevalent and a significant contributor to morbidity and mortality from gastroenteritis and extraintestinal disease. Yet, no directed antivirals or vaccines are available to treat or prevent these infections. This is in large part because these viruses are severely understudied. Most knowledge available is about classical HAstVs, with very little being known about novel HAstVs, since the former were discovered over three decades earlier. Whereas the new human astrovirus subtypes have been recently associated with central nervous system infection, we believe that human astroviruses as causative agents for central nervous system infections should be considered more often, especially in children and infants with preceding gastroenteritis.

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الفيروس النجمي البشري وعلاقته بالتهاب المعدي المعوي والتهاب الدماغ

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الملخص

يعتقد أن أحد أهم أسباب التهاب المعدة والأمعاء الحاد الفيروسي لدى الأطفال هو الفيروسات النجمية البشرية. ومع ذلك، فقد ثبت مؤخرا أن هناك تباين شديد بين الفيروسات النجمية البشرية التي تسبب الإسهال المستمر والالتهابات خارج الأمعاء والتي تصيب الانسان، وبالتالي فان تأثير ذلك على قدرة الظهارة المعوية على العمل كحاجز وتؤدي الى ضعف أطراف الزغيبات الدقيقة على العمل.

وفقا للتقارير عن حالات مميتة من التهاب السحايا والتهاب الدماغ، تم عزل كل من الفيروس النجمي VA1/HMO-C (VA1; mamastrovirus 9) والفيروس النجمي البشري الكلاسيكي 4 (HAstV4; mamastrovirus 1) من حالات التهاب الدماغ البشري. باستخدام الخلايا العصبية الأولية البشرية، والخلايا النجمية الأولية البشرية، وغيرها من خلايا الجهاز العصبي، ومن المهم تحديد قدرة هذين النمطين الجينيين للفيروسات النجمية على العدوى، التكاثر وسعة نطاق المرض، خاصة عند الأشخاص الذين يعانون من ضعف في جهاز المناعة. لم يظهر لحد الان انتقال الفيروس النجمي بين البشر والحيوانات، ولكن من المحتمل أن يحدث نظرا لأن العديد من الفيروسات البشرية والحيوانية لها أوجه تشابه وراثية.

الكلمات الدالة: المقايسة الامتصاصيَّة المناعية للإنزيم المرتبط، التهاب الدماغ، الالتهاب المعدي المعوي، الفيروس النجمي البشري، تفاعل البلمرة المتسلسل.