Atypical Viral Infections in Gastroenterology

Subjects: Virology

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Enteric viruses are commonly found obligate parasites in the gastrointestinal (GI) tract. These viruses usually follow a fecal-oral route of transmission and are characterized by their extraordinary stability as well as resistance in high-stress environments. Most of them cause similar symptoms including vomiting, diarrhea, and abdominal pain. In order to come in contract with mucosal surfaces, these viruses need to pass the three main lines of defense: mucus layer, innate immune defenses, and adaptive immune defenses. The following atypical gastrointestinal infections are discussed: SARS-CoV2, hantavirus, herpes simplex virus I, cytomegalovirus, and calicivirus. Dysbiosis represents any modification to the makeup of resident commensal communities from those found in healthy individuals and can cause a patient to become more susceptible to bacterial and viral infections. The interaction between bacteria, viruses, and host physiology is still not completely understood. However, with growing research on viral infections, dysbiosis, and new methods of detection, people are getting closer to understanding the nature of these viruses, their typical and atypical characteristics, long-term effects, and mechanisms of action in different organ systems.

Keywords: enteric viruses ; SARS-CoV-2 ; hantavirus ; dysbiosis ; microbiome ; gastrointestinal tract

1. SARS-CoV-2

Today, the COVID-19 outbreak represents one of the most significant worldwide threats to public health. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in a patient in Wuhan City, Hubei Province, China [1]. This patient had an unusual case of pneumonia. The first cases appeared in early December 2019. By the end of the month, the World Health Organization (WHO) regional office in Beijing noticed several other cases in Wuhan City that had similar symptoms [2].

The high-risk groups of this infection were noticed to be older male patients who have cardiovascular diseases, hypertension, or diabetes [3]. The infection occurs during breathing or in direct contact with droplets and aerosols that contain the virus and usually happens when the infected person coughs or sneezes. The virus in the nasal cavity then goes into the epithelial cells of the host. This entry into the epithelial cells is possible because of angiotensin-converting enzyme 2 (ACE2) receptors. These receptors can commonly be found on epithelial cells that line the digestive tract and the respiratory system [4][5].

Since the apical sides of lung epithelial cells in the alveolar space have a high expression of the ACE2 receptor, SARS-CoV-2 can quickly enter and destroy these cells. This is in concordance with the fact that many early cases of lung damage caused by these infections can be seen in the distal airways. When it comes to the innate immune response in the airway, the primary cells involved include epithelial cells, dendritic cells, and alveolar macrophages, that fight viruses before adaptive immunity [6].

Interestingly, young children and infants are usually at high risk for hospital admissions because of potential respiratory infections. However, in COVID-19 patients, recent data shows that pediatric patients have generally milder symptoms when compared to older patients. There is a strong correlation between the severity of COVID-19 and the amount of viral loads. Since children can have less viral load in these infections, this could explain the difference in severity [7]. Many hypotheses try to explain this. The first hypothesis suggests a difference in expression levels of the ACE2 receptor in these two age groups. The ACE2 receptor is usually more abundantly expressed in well-differentiated ciliated epithelial cells. This could explain why pediatric cases exhibit milder symptoms [8].

Moreover, the ACE2 expression could explain differences in disease severity among different gender groups. ACE2 gene can be found on the X-chromosome. Men have higher circulating ACE2 levels than women [9]. This could explain the differences in disease severity and mortality between men and women [10][11].

More specifically, immunofluorescent techniques show that the ACE2 receptor is abundantly expressed in glandular cells of the rectal, duodenal, and gastric epithelia. On the other hand, the esophageal epithelium composed of squamous cells has fewer expression levels of the ACE2 receptor when compared to glandular cells [12]. Additionally, the ACE2 receptor is expressed in cholangiocytes and hepatocytes, which could explain a potential association between COVID-19 infection and liver complications [13].

The symptoms of COVID-19 can range from mild to severe illness and even, in some cases, death [14]. Even though the most common symptoms of this virus include shortness of breath, fever, and a dry cough, there have also been cases in which patients experience gastrointestinal symptoms [15]. For COVID-19, gastrointestinal symptom manifestations are approximately 11% to 53%. Additionally, almost half of the patients experienced at least one symptom such as diarrhea, abdominal pain, nausea, and vomiting [16]. In severe cases, the infection can lead to multiple organ failures, especially in respiratory cases [17].

2. Hantavirus

Hantavirus belongs to the family *Bunyaviridae* [18]. They possess three negative-sensed RNA segments including small, medium, and large segments. These segments are responsible for coding RNA-dependent RNA polymerase, surface envelope proteins G1 and G2, and nucleocapsid protein. These viruses also possess a spherical lipid envelope [19].

This is a rare virus that can attack humans and causes human pulmonary syndrome (HPS) and hemorrhagic fever with renal syndrome (HFRS). Information about the symptoms that possibly occurred due to this virus date back to the first millennium and the Middle Age in England and China [20][21]. The mortality rate of hemorrhagic fever with renal syndrome and HPS is around 12% and 40%, respectively [22]. The risk groups are immunocompromised patients [23].

This virus can be spread through rodents. A person can get infected if they inhale aerosols contaminated with the virus in the form of rodent excreta [24]. Because of this, some studies suggest that people who live near infected rodents have a higher chance of getting infected [25][26].

HCPS can lead to cardiovascular irregularities and pneumonia. HFRS is characterized by hemorrhagic manifestations and renal failure. The hemorrhagic manifestations can range from petechiae to intense internal bleeding [27]. The incubation period for HFRS is usually between 10 days to 6 weeks. This is then followed by a febrile phase in which nonspecific symptoms such as abdominal pain, myalgia, and neurological, gastrointestinal, and cardiovascular symptoms appear [28]. It can lead to dangerous complications such as mucosal bleeding, petechiae, and epistaxis. In the later stages of the disease, pleural and gastrointestinal bleeding as well as hematuria can occur [29]. In rare cases, this can also lead to spleen hemorrhage [30] and even panhypopituitarism [31].

3. Herpes Simplex Virus

Herpes simplex virus belongs to the genus *Simplexvirus* subfamily *Alphaherpesvirinae* in the family *Herpesviridae* [32]. There are four main parts of a mature herpes simplex virus, including an outer membrane envelope, a core that contains the viral DNA, an icosahedral capsid as well as the tegument. The outer membrane envelope possesses many glycoprotein spikes, and the tegument has specific additional viral proteins needed for the proper functioning of the virus. Moreover, the virus contains a double-stranded DNA viral genome. It is secure inside the viral capsid shell [33][34][35][36].

This virus can be transmitted if a person comes in contact with contaminated bodily fluids such as saliva. The early beginnings of the infection are characterized by its replication at the site of the infection. The virus then travels to the dorsal root ganglia down an axon. This is the location where the virus achieves its latency. In this period, the virus is in a non-infectious state. At different periods, HSV-1 can reactivate itself and attack the host [37][38][39][40]. As a result of this, vesicular eruptions can appear usually in the orobial mucosa. Apart from orobial herpes, other presentations such as herpes gladiatorum, ocular herpes infection, herpes encephalitis, herpes sycosis, and herpetic whitlow can occur [41].

Although herpetic infection can affect any part of the GI tract, it most frequently affects the esophagus and anorectum [42]. Although immunocompromised people frequently experience herpes infections of the gut, this group is not the only one [43]. Herpetic esophagitis patients also have GI hemorrhage, dysphagia, chest pain, nausea, and vomiting. At the time of diagnosis, a lot of people had herpes infection that had spread. The most typical cause of nongonococcal proctitis in homosexual males is herpetic proctitis. Severe anorectal pain, tenesmus, constipation, discharge, hematochezia, and fever are typical symptoms of patients. Along with inguinal lymphadenopathy, concomitant neurologic symptoms such trouble urinating and paresthesias in the buttocks and upper thighs are extensively characterized [44]. The most frequent

gross esophageal finding is an ulcer, which is frequently accompanied by an exudate. However, a nonspecific erosive esophagitis affects many people. Perianal vesicles are frequently present in herpetic proctitis. Mucosal friability and ulceration are examples of cytological findings. Vesicles can occasionally be detected in the anal canal or rectum [45].

No matter the location, localized ulceration, neutrophils in the lamina propria, and an inflammatory exudate that frequently incorporates shed epithelial cells are typical histologic findings. Additionally, crypt abscesses and perivascular lymphocytic cuffing may be detected in the anorectum. Only a small percentage of biopsy specimens include multinucleate large cells and distinctive viral inclusions. The squamous epithelium near ulcer margins and sloughed cells in the exudate are the ideal places to look for viral inclusions. Among all diagnostic tools, viral culture is the most useful. Specific techniques include in situ hybridization and immunohistochemistry. Other viral infections that might affect the GI tract, such as CMV and varicella-zoster, are primarily included in the differential diagnosis. When herpetic infection is present, mixed infections are frequently seen. Herpetic infections frequently self-limit in immunocompetent patients, but they can spread and cause life-threatening sickness in immunocompromised people [46].

4. Cytomegalovirus

Immunocompetent and immunocompromised individuals can contract cytomegalovirus (CMV) infection anywhere in the GI tract. In individuals with a compromised immune system, such as those with AIDS, and following solid organ or bone marrow transplantation, CMV is best known as an opportunistic virus. In healthy individuals, first infections typically resolve on their own. The patient's immune system and the infection site influence the symptoms. The most typical clinical signs are weight loss, fever, stomach pain, and diarrhea (either bloody or watery). Hypertrophic gastropathy and protein-losing enteropathy, similar to Ménétrier's disease, are rare but significant conditions connected to pediatric CMV infection [47].

Additionally, chronic GI conditions such as Crohn's disease and ulcerative colitis may have secondary CMV added. In these circumstances, CMV superinfection is linked to steroid-refractory sickness, toxic megacolon, and a greater mortality rate in addition to exacerbations of the underlying illness. Immunohistochemistry testing for CMV is advised by certain experts as part of the routine analysis of biopsies in patients with steroid-refractory ulcerative colitis [48].

A stunning array of gross lesions are brought on by CMV. The most typical type is ulceration. There may be one or more ulcers, which may be shallow or deep. Linear ulcers and segmental ulcerative lesions might resemble Crohn's disease. Mucosal bleeding, pseudomembranes, and obstructive inflammatory masses are some other gross abnormalities. The CMV infection has a broad histologic spectrum, ranging from hardly noticeable inflammation to profound ulcers with apparent granulation tissue and necrosis. Routine H&E preparations may reveal distinctive "owl's eye" viral inclusions, which can either be intracytoplasmic or intranuclear [47]. It is more common to find inclusions in stromal and endothelial cells than in epithelial cells. CMV inclusions are frequently detected deep in ulcer bases as opposed to the borders of ulcers or the surface mucosa, unlike adenovirus and herpes. Adjacent nuclei might be more prominent, look smeared, or look like ground glass, but they do not have the usual inclusions. Cryptitis, a mixed inflammatory infiltrate that often contains many neutrophils, and mucosal ulceration, is associated with histologic findings [49].

It is possible to notice multiple apoptotic enterocytes and crypt abscesses, crypt atrophy, and crypt loss. Immunocompromised patients may develop distinctive inclusions with essentially no concomitant inflammatory reaction. When only a few unique inclusions are observed in biopsy specimens, the diagnosis could be easily overlooked. Immunohistochemistry and multilevel examinations may be extremely helpful in locating the seldom cells that have inclusions. Viral culture, PCR assays, in situ hybridization, serologic analyses, and antigen tests are other diagnostic tools. However, the presence of CMV in culture does not necessarily indicate a current infection since the virus might be excreted for months to years following primary infection [47].

Other viral infections, particularly adenoviruses, are primarily included in the differential diagnosis of CMV. Adenovirus inclusions are often intranuclear, crescent-shaped, and typically seen in the surface epithelium. CMV inclusions naturally occur in stromal or endothelial cells, have an "owl's eye" shape, and can be seen in the nucleus or cytoplasm. The most striking similarity between CMV and adenovirus infection occurs during the ballooning degeneration stage, right before cell lysis [50].

Given the similarity of the clinical and histologic characteristics, distinguishing between CMV infection and graft-versus-host disease in recipients of bone marrow transplants may be particularly challenging. In this situation, it is best to rule out CMV infection using immunohistochemistry or in situ hybridization investigations because delaying antiviral medication if CMV infection is not detected. Additionally, various ailments might coexist. When there is a lot of apoptosis, crypt

necrosis, and dropout, and there is not much inflammation, graft-versus-host disease is more likely to occur. Graft-versus-host disease is made more likely by the presence of active nests of endocrine cells [49].

5. Calicivirus

Caliciviridae represents a family of positive-sense single-stranded RNA viruses that infect both humans and animals. Phylogenetically speaking, these viruses can be divided into the following genera: Lagoviruses, Vesiviruses, Sapoviruses, and Noroviruses [51]. Sapoviruses and Noroviruses are the most common genera that cause acute gastroenteritis [52][53].

In recent decades, an increased prevalence of gastroenteritis has been noticed worldwide. A higher mortality rate has also been seen in developing countries. Apart from this, gastroenteritis outbreaks can occur in institutions such as hospitals [53][54][55][56]. A large number of these outbreaks have occurred due to contaminated food [54].

Noroviruses follow an oral-fecal transmission route, but a few airborne transmission cases have also been reported. The infection dose of these viruses is very low, and the incubation period is from 10 to 51 h. One-third of infected individuals shed the virus before the symptoms occur [57].

Human norovirus is sometimes referred to as “stomach flu” or “winter vomiting disease”. From 2006 to 2010, CDC reported that more than half of outbreaks caused by foodborne diseases were associated with this virus. During this period, the European Union also reported a large number of infections caused by this virus [58].

The most common symptom in adults is vomiting [59]. A large number of patients also sometimes have only short-term and mild symptoms that can be suppressed by oral hydration, rest, and intravenous replacement of electrolytes. However, complications can arise in the elderly and infants since they are more sensitive to volume depletion. Additionally, complications are also seen in immunocompromised patients who have received an organ transplant. This is especially seen in infants with intestinal transplants. They often experience symptoms such as persistent diarrhea. If this occurs, their immunosuppressive therapy is usually reduced [60].

Sapovirus infection outbreaks have also been more frequent in recent years [61]. When compared to noroviruses, sapoviruses cause milder symptoms, but like noroviruses, immunocompromised patients, infants, and the elderly are more prone to hospitalization [62][63]. On top of that, there are also differences in their most common symptoms. For sapoviruses, the most common symptom is diarrhea as opposed to noroviruses which usually cause vomiting, and low-grade fever [64]. In **Table 1**, the comparison between the mentioned viruses is shown.

Table 1. Comparison of virus characteristics. Data from [3][15][16][23][28][29][30][31][41][43][44][45][46][47][53][54][55][56][61].

Atypical Viral Infection	Genetic Material	Symptoms		Risk Groups
		Common	Rare	
SARS-CoV-2	RNA	Shortness of breath [15] Fever [15] Dry cough [15]	Diarrhea [16] Abdominal pain [16] Nausea [16] Vomiting [16]	Older males with cardiovascular diseases, hypertension, or diabetes [3]
Hantavirus	RNA	Abdominal pain [28] Myalgia [28] Neurological [28]	Mucosal bleeding [29] Epistaxis [29] Spleen hemorrhage [30] Panhypopituitarism [31]	Immunocompromised patients [23]
HSV	DNA	Herpes [41] Ulcer [45] Chest pain [44] Fever [44]	Multinucleated large cells [46] Distinctive viral inclusions [46]	Immunocompromised patients [43]
CMV	DNA	Weight loss [47] Fever [47] Stomach pain [47] Diarrhea [47]	Hypertrophic gastropathy [47] Protein-losing enteropathy [47]	Immunocompromised patients [47]
Calicivirus	RNA	Diarrhea [61] Vomiting [61] Gastroenteritis [53][54][55][56] Low-grade fever [61]	/	Infants [61] Immunocompromised patients [61] Elderly patients [61]

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