REVIEW
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Neurotropic enteroviruses (Picornaviridae: *Enterovirus*): predominant types, basis of neurovirulence

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Abstract
Enteroviruses are one of the most common causative agents of infectious diseases of the central nervous system. They are characterized by genetic variability, the ability to infect a wide range of cells, including brain microglial cells and astrocytes, and persist in the central nervous system tissue, causing delayed and chronic diseases. The review presents data on the basis of neurovirulence of non-polio enteroviruses and the most common pathogens causing enteroviral neuroinfections.

Keywords: *non-polio enteroviruses; enteroviral neuroinfections; serous meningitis; acute flaccid paralysis*

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НАУЧНЫЙ ОБЗОР
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Нейротропные энтеровирусы (Picornaviridae: *Enterovirus)*: доминирующие типы, основы нейровирулентности

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Резюме
Энтеровирусы являются одной из наиболее частых причин инфекционных заболеваний центральной нервной системы (ЦНС). Их объединяет генетическая вариабельность, способность инфицировать широкий спектр клеток, в том числе клетки микроглии мозга и астроциты, а также персистировать в ткани ЦНС, обусловливая отсроченные и хронические заболевания. В обзоре представлен материал об основах нейровирулентности неполиомиелитных энтеровирусов и наиболее распространенных возбудителях энтеровирусных нейроинфекций.

Ключевые слова: *неполиомиелитные энтеровирусы; энтеровирусные нейроинфекции; серозный менингит; острые вялые параличи*

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Финансирование. Исследование проведено на средства федерального бюджета, выделенные на финансирование отраслевой научной программы Роспотребнадзора.
Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Introduction

The *Enterovirus* genus, a member of the large and diverse *Picornoviridae* family, is subdivided into 15 species: *Enterovirus A–L* and *Rhinovirus A–C*. Among non-polio enteroviruses (NPEVs), *Enterovirus* species *A–D*, including more than 100 antigenically and genetically distinct types, are pathogenic for humans. The *Enterovirus A* species includes 25 types, the most numerous *Enterovirus B* species combines 63 types, *Enterovirus C*

species includes 23 types, and *Enterovirus D* species includes 5 types[1]. Enteroviruses are small (about 30 nm in diameter) non-enveloped viruses with a 7,500 nucleotide single-stranded RNA genome of positive polarity and a single open reading frame flanked by 5'- and 3'-untranslated regions (UTRs). Viral RNA replication is catalyzed by RNA-dependent RNA polymerase, an error-prone enzyme lacking proofreading activity which causes a high frequency of mutations and determines the genetic diversity of enteroviruses [1]. The high genetic plasticity of enteroviruses additionally creates the risk of highly virulent strains capable of realizing their neurogenic potential, provoking large-scale disease outbreaks. The most etiologically significant neurotropic NPEVs are representatives of the *Enterovirus B* species (CVB1-5, CVA9, ECHO 6, 7, 9, 30, etc.). *Enterovirus A* NPEVs (EV-A71, CA2, CVA6, CA10 and CVA16, etc.) are mainly associated with exanthem forms of enterovirus infection, which may be accompanied by severe neurological complications. *Enterovirus D68* (EV-D68) is associated with a number of outbreaks and sporadic cases of acute flaccid paralysis (AFP). Less frequently, *Enterovirus C* NPEVs are the cause of neuroinfections of enterovirus etiology [2, 3]. Infection of different anatomical regions of the central nervous system (CNS) causes a variety of clinical forms of neuroinfections (meningitis, encephalitis, AFP, meningoencephalitis, encephalomyelitis, etc.) [4, 5]. Serous meningitis (lesion of the hard or soft cerebral membranes) is the most frequent among infectious CNS diseases of viral etiology [6–8]. NPEVs are associated with 85–90% of all cases of serous meningitis; these enteroviruses are also capable of causing encephalitis, AFP, and other forms of diseases with varying degrees of severity: from mild forms to severe lesions of the cardiovascular system and CNS [9–11].

The objective of this review is to analyze the current information on the most common pathogens of enterovirus neuroinfections and the basis of NPEV neurovirulence.

Predominant types of neurotropic enteroviruses

Enterovirus B neurotropic viruses (EVBs). The greatest number of group and sporadic cases of enterovirus serous meningitis (EVM) is associated with NPEVs of the **EVB** species, among which the most common at present in temperate climates is the virus ECHO30 (**E30**). Phylogenetic analysis based on complete nucleotide sequences of the *1D* gene encoding the major capsid protein VP1 showed extensive genetic diversity of E30 strains represented by 8 genotypes. The existence of three major phylogenetic clusters of E30 virus formed by genotypes a/b, c and d/e/f/g/h was shown, within which subtypes are differentiated: E30f is subdivided into subtypes C3-5 and E30e into subtypes C0, C1, C2 [12]. Outbreaks and sporadic cases of EVM caused by E30 have been regularly recorded in Europe, China (mainly eastern provinces), the USA, Brazil, and Russia since the beginning of the 21st century [13]. In Russia, the largest outbreaks of E30-associated meningitis were registered in 2003, 2006–2009 (Khabarovsk Krai, Nizhny Novgorod, Novgorod, Arkhangelsk regions and a number of other territories), in 2013 (a number of territories of the Northwestern Federal District (NWFD): Novgorod and Vologda regions, St. Petersburg) and in 2017 (Khanty-Mansiysk Autonomous District – Yugra, Tyumen region). Type E30 enteroviruses isolated during the 2008–2009 outbreak belonged to the eC2 genotype, which was common in Russia at that time. The E30 strains circulating in the NWFD during the 2013 and 2017 outbreaks belonged to different cell lines of the E30h genotype [14–16].

Outbreaks and sporadic cases of **E9**-associated serous meningitis are regularly recorded. In the United States, according to epidemiologic surveillance data, from 1970 to 2005, E9 was the most common type detected in EVM of established etiology [17, 18]. In 1992, E9 was the etiologic cause of a large outbreak of viral meningitis in western Australia, and in 2009–2010, it was first identified as the most common type in the sporadic incidence of serous meningitis in Southwest China [19]. During the same period, E9 caused a seasonal rise in the incidence and a number of EVM outbreaks in several regions of Russia [20].

In 2006, **E6** virus was the pathogen of a large outbreak of serous meningitis in Khabarovsk Krai [21]. In 2010–2012, E6 prevailed as the pathogen of serous meningitis in the Moscow region, with E30 no longer being the most common type [22], and was also the main pathogen isolated from patients with CNS infections between 2007 and 2012 in southern Australia [23]. Enterovirus infections in young children caused by virus types E6 and E9 are often severe and in some cases fatal [18].

Coxsackie virus B5 (**CVB5**) infection can lead to encephalitis, AFP, pancreatitis and certain chronic diseases. This virus is among the most frequent causes of serous meningitis outbreaks worldwide: The United States (1961, 1972, and 1983), Greece (1999, 2001), and Belgium (2000). In China, the largest outbreaks were reported in Shandong Province in 2005 and 2009 and several other provinces in 2009–2012 [24].

Other viruses of the *Enterovirus B* species associated with outbreaks and sporadic cases of EVM include **E13** (Germany, Spain, 2000), **E11** (Greece, 2003–2005), which poses a particular threat to newborns, and **E4**, identified as an etiologic cause of serous meningitis in Africa (Pretoria, 2010–2011, Western Cape and Eastern Cape provinces of South Africa, 2018–2019) and Europe (Finland, Sweden, Norway, Denmark, Iceland and Germany, 2013–2014) [25–27].

E18 virus is considered a frequent pathogen of serous meningitis. Large outbreaks of E18-associated EVM have been reported in the United States (2000–2001) and Taiwan (2006) [28]. In 2013– 2015 (Hebei Province, China), E18 was the most common type detected in children with viral meningitis and encephalitis. In Russia, E18 became the prevalent pathogen of EVM for the first time in a separate territory in 2017 (Saratov region) [29].

[1]Picornavirus Home. Available at: http://www.picornaviridae.com/

Coxsackie virus A9 **(CVA9)** rarely acts as the most common variant but regularly causes sporadic cases of EVM worldwide. CVA9-associated outbreaks were reported in 2010 (Alberta, Canada) and 2015–2016 (Mossel Bay, South Africa) [30, 31].

The severity of clinical manifestations of EVB infection is associated with the age of patients. In newborns and young children, the disease is usually more severe, which some researchers attribute to the immune system not being fully developed and the peculiarity of enterovirus receptor expression in the cells of the developing brain [32].

Enterovirus A neurotropic viruses. The most significant virus in infectious neuropathology is enterovirus A71 (**EV-A71**), which is known as the major etiologic cause of outbreaks of hand, foot and mouth disease (HFMD). The disease can be complicated by severe neurologic manifestations ranging from viral meningitis, AFP, and encephalitis to systemic disorders including pulmonary edema and cardiorespiratory collapse. Based on the variability of the gene encoding the capsid protein VP1, 8 EV-A71 (A–H) genotypes are distinguished [32]. Genotype A is represented by a single prototype strain (BrCr) isolated in 1969 and several strains that resumed circulation in mainland China in 2008–2010. Genotypes B and C are subdivided into 6 subgenotypes (B0–B5 and C0–C5, respectively). EV-A71 subgenotypes B4, B5 and C4 circulate mainly in East and Southeast Asia, whereas C1 and C2 are predominant in Europe. Genotypes D and G have been identified in India, while genotypes E, F and H have been identified in Africa, Madagascar and Pakistan, respectively [2, 34]. The most severe forms of HFMD are associated with EV-A71 subgenotypes C4 and B5 circulating mainly in Southeast Asia [35].

EV-A71 was first isolated in 1969 from children with meningitis and encephalitis in the United States. Over the next few years, EV-A71 spread throughout the Americas, Europe, and other countries, causing small outbreaks and sporadic cases, with the exception of a few large outbreaks reported in 1975 in Bulgaria and in 1978 in Hungary [36, 37]. Large-scale outbreaks of HFMD occurred in the Asia-Pacific region in the late 20th and early 21st centuries. From 2008 to 2015, about 13.7 million cases of HFMD were reported in mainland China, among which 3322 were fatal, 93% of cases were etiologically associated with EV-A71 [33]. Three inactivated EV-A71 vaccines derived from virus genotype C4 have proven effective against EV71-associated HFMD in children aged 6–35 months. From 2016 to 2020, during EV-A71 epidemics in mainland China, with the use of EV-A71 vaccines, approximately 9.5 million cases were reported, including 358 fatal cases, indicating a significant reduction in mortality due to vaccination [38, 39].

Until 2013, EV-A71 was isolated sporadically on the territory of Russia. In June 2013, an outbreak of EVI associated with the circulation of EV-A71 subgenotype C4 was registered in Rostov-on-Don among preschool children. The diseases were characterized by an acute onset with symptoms of intoxication syndrome and HFMD as well as subsequent development of CNS pathology (meningitis, meningoencephalitis) in 37.4% of patients [40, 41].

Coxsackie A10 (**CVA10**) infection with severe CNS lesions has noticeably increased in the last decade. In Shanghai (China) in 2016 and 2018, the frequency of CVA10 detection in patients with meningitis, encephalitis, and meningoencephalitis increased significantly [42]. In 2017, a significant rise in the number of CVA10-infection cases was observed in the subjects of the Far Eastern Federal District of the Russian Federation with an increase in the proportion of enterovirus meningitis. Cases of CVA10-associated AFP were registered in 2009–2017 in the territory of India [43].

Coxsackie virus A2 (**CVA2**), primarily associated with vesicular pharyngitis, HFMD, pleurodynia, myocarditis, and type 1 diabetes, is occasionally detected in patients with meningitis, encephalitis, and AFP, which are accompanied by persistent movement disorders clinically similar to paralytic poliomyelitis. In a study conducted in Brazil as part of poliomyelitis surveillance from 2005 to 2017, CVA2 was one of the predominant types of NPEVs detected in patients with AFP. During the 20-year period of surveillance for AFP in the Russian Federation, 5 cases of AFP associated with CVA2 enterovirus were identified [44]. In 2012. CVA2 caused an outbreak of severe respiratory illness in Hong Kong, which included 2 fatal cases. In 2014, an outbreak of CVA2-associated AFP was reported in Taiwan [45].

*Enterovirus C (**EVC**) neurotropic viruses.* Several types of *Enterovirus C* species have been associated with outbreaks of AFP, encephalitis, meningitis and HFMD. Enterovirus EV-C105 has been the etiologic cause of AFP outbreaks in India and New Zealand. EV-C96, first isolated in 2000 from an AFP patient in Bangladesh, has been detected in Finland, Slovakia, the Philippines, Cambodia, China, and Bolivia in subsequent years from both AFP patients and healthy individuals [46].

Neurotropic viruses of the species Enterovirus D. **EV-D68** have been associated with sporadic cases and a number of outbreaks of AFP. EV-D68 was first isolated in 1962 from children with pneumonia. It is primarily a respiratory virus causing nasal congestion, cough, sore throat and fever. In 2014, the first major outbreak of severe respiratory EV-D68-associated severe respiratory AFP occurred in North America. Small foci of EV-D68 infection have also been reported in Europe and Asia. An increase in the number of EV-D68 infected cases with neurological symptoms was observed in Sweden, the Netherlands, Italy, and the United States in 2016. The United States also had such an increase in the year 2018. In Japan, an increase in EV-D68 activity was reported in 2013 and 2015 [47–49].

Basics of neurovirulence of enteroviruses

The mucous membranes of the oropharynx and gastrointestinal tract serve as entry points for enteroviruses in the human body, where primary replication takes place in the oropharyngeal and mesenteric lymph nodes. When the virus enters the cells of the reticuloendothelial system and bloodstream, primary viremia develops, contributing to

the penetration of viruses into various organs and tissues: nervous system, myocardium, liver, pancreas, etc. [50]. The penetration of viral particles from the bloodstream into the CNS is prevented by the blood-brain barrier (BBB), which is a highly selective filter between brain cells and blood vessels. The integrity of the BBB can be disrupted both as a result of direct infection of endothelial cells of brain capillaries that make up its structure and under the influence of cytokines that increase BBB permeability and are produced by activated CNS microglia cells in response to viral infection [51, 52]. It is assumed that in the developing brain, microglia are constantly in an activated state, which confirms the hypothesis about the influence of the functional state and maturity of the CNS immune system on the severity of neurological symptoms in EVI [53].

Enteroviruses are capable of penetrating the CNS by infecting a wide range of peripheral circulating immune cells, which serve as a Trojan horse for their delivery to CNS tissue. Cerebrospinal fluid contains a mononuclear cell population consisting of T cells (~ 90%), B cells (~ 5%), monocytes (~ 5%), and dendritic cells (< 1%) that are potential vectors of enteroviruses. After entry of mononuclear cells into the CNS, enteroviruses are released and infect neuroglia and brain neurons, realizing their neurogenic potential [54]. Certain neurotropic enteroviruses are able to engage in retrograde axonal transport and penetrate into the CNS through peripheral nerve terminals, as experimentally demonstrated for the neurotropic viruses EV-A71 and EV-D68, which penetrate into the CNS when infecting peripheral spinal motor neurons. Having undergone endocytosis at the terminal end of the axon, enterovirus particles travel to the neuron body in a retrograde direction via dynein-mediated vesicular transport [55]. Thus, there are several alternative methods for enterovirus entry into CNS cells.

It is hypothesized that genetic variants of enterovirus that differ in their ability to penetrate CNS cells may be formed during replication. Different quasispecies of the virus have been detected in respiratory, intestinal tract and CNS samples isolated from EV-A71 infected patients. *In vitro* studies showed that the quasispecies variants predominant in CNS samples replicated most efficiently in neuronal cells. It is suggested that the proportion of different variants within quasispecies may determine the dynamics of the clinical picture. In terms of identifying genetic variants with increased neuroinvasive ability, further study and characterization of quasispecies isolated from different clinical samples in mild and severe forms of enterovirus neuroinfection is a topic of interest [10, 56].

Depending on the tropism to specific cells and tissues, enteroviruses can affect different anatomical parts of the CNS which causes different clinical forms of neuroinfection. Meningoencephalitis that develops as a result of EV-A71 lesions of the brain stem can disrupt the regulation of cardiovascular and respiratory activity and subsequently lead to neurogenic pulmonary edema and heart failure [57]. In an experiment with newborn mice, it was shown that Coxsackie virus A3 can cause focal lesions in the right frontal lobe of the brain, leading to the development of encephalitis, and Coxsackie virus B and certain types of echoviruses can infect various regions of the cerebral cortex and hippocampus, causing the development of spastic paralysis [58].

An important factor that determines the neurotropic properties of the virus is the activity of IRES (Internal Ribosome Entry Site) regulatory elements. It has been shown that mutations in the IRES lead to translation defects and a decrease in the level of enterovirus replication, including in the CNS [59]. The differential susceptibility of tissues to enterovirus infection may also be determined by the antiviral activity of the innate immune system. It is assumed that the α/β-interferon system limits enterovirus replication in extraneural tissues and prevents its penetration into the CNS [60].

The efficiency of enterovirus entry into host cells is determined by the availability and level of expression of specific enterovirus surface receptors. One of the distinctive features of NPEVs is the diversity of these receptors. For example, unlike polioviruses that use a single receptor (glycoprotein CD155) for entry, enterovirus EV-A71 utilizes several receptors for binding to the cell surface, including hSCARB2, hPSGL1, Anx2, heparan sulfate, vimentin, human tryptophanyl-tRNA synthetase, and others. The vast number of receptors allows the virus to infect a wider range of cells, use different pathways for routing virus-containing endosomes in the host cell and explains the polymorphism of clinical symptoms caused by EV-A71 [10, 61].

The unique tissue tropism of NPEV is also manifested in its ability to infect neuronal progenitor cells and astrocytes. The loss of neural progenitor cells capable of differentiating into neuronal lineages, astrocytes and oligodendrocytes, leads to decreased neurogenesis, delayed development of the nervous system and impaired cognitive function, memory and learning. The area of localization of astrocytes in the brain is much wider than that of neural progenitor cells, due to which infection of astrocytes along with their ability to mitosis creates a reservoir for viral proliferation and promotes effective virus spread in the CNS. The ability to infect astrocytic cultures has been demonstrated for many types of enteroviruses: EV-A71, CVA9, CVB3, CVB4, and EV-D68 [10, 62].

Another feature of neurotropic enteroviruses is their ability to persist in CNS tissues for a long time, which many researchers associate with the development of such delayed diseases as post-polio syndrome, schizophrenia, amyotrophic lateral sclerosis, insulin-dependent diabetes, chronic viral cardiomyopathy, chronic enteroviral meningoencephalitis, and the multisystem disease myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [63, 64]. Persistent infection is thought to be due to the selection of mutant forms of the virus that have less pronounced cytopathic properties, which is part of the coevolution of enteroviruses and body cells, which in turn limit the spread of infection by reducing the expression of entry receptors [65]. However, the exact mechanisms of this phenomenon are still unknown.

Given the great diversity of NPEVs and the wide range of diseases they cause, epidemiological surveillance of enterovirus infection is a rather complex task, for the implementation of which the European Non-Poliovirus Enterovirus Surveillance Network (ENPEN) [66], the Asia-Pacific Network for Enterovirus Surveillance (APNES), which was established through collaboration between academic institutions and hospitals in Cambodia, Malaysia, Vietnam and Taiwan [67] and has been in operation since 1961. The National Enterovirus Surveillance System (NESS) [17]. In the Russian Federation, official statistical registration of enterovirus infection was introduced in 2006. Currently, the incidence of meningitis is increasing in the Russian Federation. The detection of enteroviruses that previously caused mainly respiratory or exanthemal diseases in patients with serous meningitis and meningoencephalitis is a problem of great concern, which may indicate the probability of the emergence of new neurovirulent variants of enteroviruses.

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