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Epidemiological and clinical review on the current knowledge of EV-D68

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Abstract

Enterovirus D68 (EV-D68) is a unique non-polio enterovirus, first identified in 1962. The wide spread of the virus in recent years has posed a threat to public health. EV-D68 typically causes respiratory illness, which can be mild (like a common cold) or more severe. The studies have demonstrated the potential for EV-D68 to induce neurological disease. Epidemiologic data support an association of EV-D68 with the acute flaccid myelitis (AFM)/ acute flaccid paralysis (AFP), although the mechanism remains unclear. AFM a rare, but serious neurological condition. Children are at the greatest risk of severe infection and most cases occur in children under the age of 5. EV-D68 can be detected in respiratory specimens and rarely in cerebrospinal fluid.

Keywords: EV-D68; Respiratory tract infections; Acute flaccid myelitis; Acute flaccid paralysis

1. Introduction

Enterovirus D68 (EV-D68) is a respiratory and neurovirulent human pathogen that was first isolated by Schieble et al. in the USA (California) in 1962 from respiratory specimens of four hospitalized children with lower respiratory tract (LRT) infection. EV-D68 belongs to genus Enterovirus, family Picornaviridae. This virus, unlike other enteroviruses, is primarily detected in association with respiratory disease and shows similar biology to some rhinoviruses [1]. It has an RNA genome, 4 structural proteins (VP1-VP4) and 7 non-structural proteins (2A, 2B, 2C, 3A, 3B, 3C, 3D). The most common EV-D68 subgenotype/clade that circulates worldwide is B3, followed by A2/D2 [2]. The VP1 capsid protein plays a major role in receptor binding [3]. Once in the upper respiratory tract (URT), the virus uses the “canyon” of VP1 to bind to sialic acid (SA), which serves as a major cellular receptor. More recent studies have shown that in the absence of sialic acid (or a sialylated glycoprotein), EV-D68 can use other alternative unsialylated receptors, such as sulfated glycosaminoglycans. Furthermore, intercellular adhesion molecule 5 (ICAM-5) has been identified as an additional neuron-specific receptor for the virus [4]. In general, EV-D68 can use different functional receptors to enter the host cell, and their expression varies in different tissues. After attachment to a cell, the virus is internalized by endocytosis. Viral replication occurs in the cytoplasm. The fact that EV-D68 has been detected in samples from URT and LRT suggests that this virus can replicate throughout the respiratory tract. The cellular tropism of EV-D68 in URT has been investigated using in vitro and in vivo models. In vitro, EV-D68 infects predominantly ciliated epithelial cells, causing cell lysis and induction of multiple proinflammatory cytokines. Nonstructural viral proteins 3C and 2A have been shown to play a role in suppressing innate immune responses in vitro [5]. The immunopathogenesis of enterovirus infection is not fully understood. EV-D68 is acid labile, with an optimal replication temperature of 33 °C. These characteristics could most likely explain the predilection of EV-D68 for the respiratory rather than the gastrointestinal tract, making this virus more similar to rhinoviruses than enteroviruses. Its transmission is via respiratory aerosols.

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2. Epidemiological and clinical characteristics EV-D68 infection

EV-D68 has been increasingly recognized as an emerging virus, with outbreaks occurring primarily in children. The full extent of EV-D68 distribution, both through time and space, remains unknown. In temperate climates, cases increase mainly during the summer–autumn season. Cases have been recorded mostly in even-numbered years, with the highest peaks in 2014, 2016 and 2018. Circulating strains of EV-D68 are genetically diverse and widely distributed worldwide. Since 2014, subclades B1 and B3 have become dominant. Different subclades have been identified in respiratory and neurological samples, with varying rates of amino acid substitutions [6].

Reports of EV-D68 identified as an etiologic agent of respiratory disease are steadily increasing, with the majority of symptomatic infections occurring in children [7]. EV-D68 infection may proceed asymptomatically or with manifestations of various clinical severity, ranging from mild and subclinical URT infections to severe pneumonia with development of respiratory failure and sometimes unfavorable outcome. EV-D68 positive patients report cough, dyspnea and wheezing more commonly. The mechanism by which children and immunocompromised adults infected with EV-D68 develop severe disease is unclear. To a large extent, children have an increased risk of developing severe disease, but reports also suggest that adults, especially those with comorbidities such as oncohematologic disease or immunosuppression, may also develop severe EV-D68-related respiratory disease [8]. Severe pneumonias caused by EV-D68 have also been described in patients without underlying diseases [9]. EV-D68 has been associated with asthma exacerbations in children.

There were 26 sporadic cases of EV-D68 reported in 1970-2005 [10]. From October 2008 to February 2009 in the Philippines, EV-D68 was identified as the causative agent of severe pneumonia in 21 of 816 (2.6%) hospitalized children aged 1 month to 9 years, with two reported deaths [11]. The virus has been detected each year in Japan since 2003; in the autumn of 2010, it was detected in 14 samples from children under the age of 5 with respiratory tract infections and in 1 sample from a child with febrile seizures [12]. One of the largest outbreaks was reported in Japan in 2010, where more than 120 cases were diagnosed [13]. In the autumn of 2010, an increase in EV-D68 infections was reported in the northern part of the Netherlands in patients with severe respiratory disease. Of the 24 cases recorded, 5 were admitted to intensive care [14]. More than 2000 cases of EV-D68 were reported in 20 countries in 2014 [15]. Since 2014, there have been dozens of reports of the global spread of EV-D68, with outbreaks in the United States and Europe showing a seasonal biennial pattern [16]. There was a large outbreak of EV-D68 in the US in 2014, with the Centers for Disease Control and Prevention (CDC) reporting 1395 people infected with the virus. In the 2014 outbreak, there were identified 7 co-circulating EV-D68 strains. The VP1 gene sequences of these 7 strains are most closely related to EV-D68 previously detected in the US, Europe and Asia [17]. During this epidemic, pediatric hospitals identified EV-D68 as a possible cause of acute neurological illness and acute respiratory dysfunction [18]. Between August and October 2014, nearly half of respiratory specimens sequenced from patients positive for enterovirus or rhinovirus were identified as EV-D68. A total of 927 cases were identified and reported to the CDC. Half of the patients had a history of asthma and most required intensive care [19]. In 2020, the first year of the SARS-CoV-2 pandemic, no EV-D68 cases were reported in Europe. It has been suggested that this is a result of the stringent measures taken to contain the pandemic and the practices of social distancing. Despite the interruption in EV-D68 circulation during the COVID-19 pandemic, EV-D68 evolution continued, resulting in the emergence of two novel post-pandemic B3-derived lineages [20]. A similar upsurge in EVD68 circulation was reported in September 2021 in Europe and was presumably related to the widespread reopening after COVID-19 lockdowns.

The mechanism by which the virus traffics from the respiratory tract into the central nervous system (CNS) is not known. The severity of respiratory disease does not appear to correlate with the risk of developing paralysis. Recent studies have shown that neurological symptoms were associated with EV-D68 subclade B3 strains [21]. In September 2014, a case of acute flaccid paralysis (AFP) after pneumonia associated with EV- D68 was reported in France [22]. Epidemiological data support the association of EV-D68 with acute flaccid myelitis (AFM)/acute flaccid paralysis (AFP). Of the various CNS complications associated with EV-D68 infection, the development of AFM is the most commonly reported. In most cases, this rare but serious neurological disease is preceded by prodromal respiratory or gastrointestinal symptoms and febrility. AFM is characterized by the sudden onset of muscle weakness in the limbs or rapidly developing flaccid paralysis in otherwise previously healthy children. Early manifestations of AFM include headache, stiffness or pain in the back and neck or affected limb. Magnetic resonance imaging (MRI) detects lesions localized primarily in the gray matter of the spinal cord. In contrast to polio, patients with AFM associated with EV-D68 are more likely to have proximal muscle groups affected. Almost all patients had diffuse myalgias and limb pain [23]. The first case of AFM etiologically caused by EV-D68 infection was reported in 2005, and the causative agent was identified in the cerebrospinal fluid (CSF) [24]. EV-D68 is the most frequently detected virus in clinical samples of patients with AFM [25]. In 2012, a total of 23 cases of AFP (mostly children and young adults) in California were reported to the CDC [26]. In 2018, a 6-year-old boy was diagnosed with EV-D68-associated AFM in China [27]. Acute myelitis

associated with EV-D68 can progress rapidly, within days or even hours after the onset of symptoms. Clinical outcomes are variable. One to four limbs may be affected with asymmetric distribution. Typically, the upper limbs are affected more commonly than the lower limbs [28]. Hypo- or areflexia has been reported in up to 80% of patients [29]. The mean age of AFM presentation is 5.8 years, with most cases in children ranging from 2 to 11.5 years with a male predominance [30]. EV-D68 infection is sometimes associated with encephalitis, meningoencephalitis, or aseptic meningitis [31]. Fatal meningomyeloencephalitis caused by EV-D68 has been reported in a 5-year-old boy with pneumonia, asymmetric flaccid paralysis, and sudden cardiovascular collapse. The initial symptoms in this child were headache, subfebrile temperature, sore throat, followed (2 days later) by myalgias, progressive muscle weakness in the upper extremities, more pronounced in the right arm [32]. This virus was identified as the cause of the fatal illness by identification and sequencing of EV-D68 in the CSF, combined with the characteristic histologic pattern of enteroviral central nervous system infection.

Viral RNA can be detected in nasopharyngeal samples, usually within the first week of disease onset [33]. Given a median duration of RNA shedding of 12 days, early respiratory sampling is key to the detection of EV-D68 in suspected cases of AFM. Inappropriate sampling may lead to underdiagnosis and underreporting of the disease. Molecular methods (real-time PCR) and virus typing by sequencing can detect the presence of EV-D68.

3. Conclusion

The past decade has witnessed the global emergence and rapid spread of EV-D68, a respiratory pathogen that causes severe respiratory illness and paralysis in children. While most enteroviruses infect the gastrointestinal tract, EV-D68 exhibits tropism for the respiratory epithelium. Children are at greatest risk for severe EV-D68 infections. In addition, central nervous system involvement with polio-like manifestations is possible. Lesions in the anterior horn of the spinal cord are associated with AFM, suggesting that motor neuron function is impaired. The diagnosis of EV-D68-associated neurological disease is challenging because the virus is rarely detected in CSF. Clinicians should consider EV-D68 infection in the differential diagnosis of AFP and respiratory failure.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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