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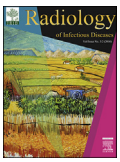

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Review

The pulmonary complications associated with EV71-infected hand–foot–mouth disease

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Abstract

Hand–foot–mouth disease (HFMD) was an acute intestinal infectious disease, which mainly occurred in the children, especially under 5 years old. Enterovirus 71 (EV71) was the most common pathogen causing HFMD, especially severe HFMD. Most patients had a good prognosis, but a few patients complicated by encephalitis, pulmonary edema, and hemorrhage, myocarditis and other complications, which may cause bad prognosis and even death. In this paper, the clinical manifestations, pathogenesis, pathology, imaging changes and treatment of pulmonary inflammation, edema and hemorrhage associated EV71- induced HFMD were reviewed.

Keywords: Enterovirus 71; Hand–foot–mouth disease; Pulmonary inflammation; Pulmonary edema; Pulmonary hemorrhage

1. Introduction

Hand–foot–mouth disease (HFMD) is an acute intestinal infectious disease, which mainly occurs in the children under 5 years old. Annually, the occurrence of HFMD is seasonal and regional, which peaks in June in north China, but has semi-annual outbreaks in May and September–October in southern China. The main pathogens include coxsackievirus A group type 16 (CVA16) and EV71. In additional, the EV71 is recognized as major pathogens responsible for severe HFMD [1–4]. The common clinical manifestations include fever, sores in the mouth, and blister-like rashes on the hands, feet, and buttocks [5]. But a few part of cases may have various delayed cutaneous findings, including onychomadesis, nail discoloration, beaus line and cutaneous desquamation [6]. Most patients may have good prognosis, but a few patients may be complicated by encephalitis, pulmonary edema, and hemorrhage, myocarditis and other complications, which may cause bad prognosis and even death [7,8].

Recently, the pathogenesis of central nervous system (CNS) damage associated with EV71-infected HFMD was the neurotropic nature of EV71, which has been recognized widely. And many previous studies had discussed the imaging manifestations of CNS damage during treatment and follow-up [9,10]. However, although many previous studies had been performed, including fatal cases report, imaging analysis, animal model studies, and so on, the pathogenesis and other aspects of pulmonary damage associated with EV71-infected HFMD are not yet clear completely [11,12]. In this paper, the clinical manifestations, pathogenesis, pathology and imaging changes of pulmonary inflammation, edema and hemorrhage associated EV71- induced HFMD were reviewed to further understand and to improve the diagnosis and treatment of pulmonary complications.

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2. EV71 and its infection routes and pathogenesis

2.1. EV71

EV71 is a small RNA virus, which is composed of single stranded positive-sense RNA and viral capsid, the viral capsid of which consists of 4 proteins, including VP1, VP2, VP3, VP4 [13]. In 1969, EV71 was first identified in patients with neurological disease in California [14]. With phylogenetic analysis, the EV71 isolates included four genotypes: A–C. And Genotype A was represented by only one isolate (BrCr-CA-70), Genotype B and C included B1–B5 and C1–C5, respectively, which showed worldwide distribution [15]. In additional, some researchers discovered the forth genotype, genotype D [16]. Since 2000, EV71 has become predominant pathogen across the Asia–Pacific region [17]. In our country, the EV71 subgenogroup C4 caused the severe forms of HFMD mostly [18]. Between 2010 and 2012, there were about 7,200,092 probable HFMD cases registered in surveillance registry in our country, in which about 0.03% of the cases were died, and 93% laboratory confirmed deaths were associated with EV71 [2].

2.2. Infection routes of EV71

EV71 could be infected via fecal-oral, respiratory, contacting with the patient's skin or liquid in mucosal herpes. Different infection routes may affect the progress of the disease. An animal experiment studied the pathogenic process of systemic EV71 infection in rhesus monkeys after inoculation via four different routes, included intracerebral, intravenous, respiratory and digestive route. They found some interesting phenomena as followed: (1) Intracerebral inoculation could led to pulmonary edema and hemorrhage, along with impairment of neurons; (2) Intravenous inoculation resulted in direct infection of the CNS, accompanied by obvious inflammation of lung tissue, as shown by impairment of the alveoli structure and massive cellular infiltration around the terminal bronchioles and small vessels. (3) respiratory and digestive inoculation caused the same pathological changes in lungs, and resulted in low levels of pathological damage to the CNS [19]. These results may suggest that pathological changes were not the same via different EV71 infection routes and the respiratory and digestive infection routes were the main infection routes.

2.3. Pathogenesis of EV71

The cytological experiment found that scavenger receptor class B member 2 (SCARB2) and P-selectin glycoprotein ligand-1 (PSGL-1) were specific receptor for EV71. SCARB2 was the receptor of all EV71, which played an important role in the early stage of EV71 infection, and the EV71 infection must have two conditions of SCARB2 receptor and acid environment. Two previous studies found EV71 receptor SCARB2 distributes in bronchial, bronchioli, alveolar epithelial and inflammatory cells of HFMD. Meanwhile, PSGL-1 only distributes in inflammatory cells of HFMD in adult patients [20,21]. Another previous study indicated that host signal transducer and activator of transcription 3 (STAT3) had an important role in EV71 infection and replication, which may be induced by the doen-regulation of phosphorylated STAT3 level. Therefore, under the action of STAT3 affects, EV71 infection increased the cellular susceptibility to the virus and promoted the viral replication [22].

3. Pulmonary inflammation associated with EV71-infected HFMD

3.1. Clinical manifestations

The patients' clinical manifestations of pulmonary inflammation associated with EV71-infected HFMD are not specificity. Some patients may have fever, pharyngeal congestion, heavy breathing, wheezing, coughing, tonsillar enlargement, headache, drowsiness or other neurological symptoms.

3.2. Pathogenesis

At present, the pathogenesis of pulmonary inflammation associated with EV71-infected HFMD was not yet clear. The possible mechanisms were as followed: EV71 virus can directly damage the lungs, because it has obvious neurotropic and dermatropic characteristic. After infected EV71 via the pharynx or intestinal, EV71 got into blood circulation, and then invaded reticuloendothelium tissue, deep lymph nodes, liver, spleen, bone marrow and other organs and tissues where EV71 was bred to large number, getting into the blood circulation again, which may cause the secondary viremia. The virus could enter the lungs with blood flow, so the lungs were damaged directly. In additional, after infected EV71, the patients' immunity activity was decreased, so the bronchial and lung tissues may be easily infected with infected other bacteria [23]. Some previous studies also supported the above theory. In their studies, they found EV71 genomic RNA in the macrophages in alveolar spaces and in the inflammatory cells in the trachea and EV71 antigenomic RNA in type II lung epithelial cells in the lungs of fatally patients confirmed EV71 infection, and EV71 antigens were marginally observed in the bronchial lining epithelial cells and alveolar macrophages in human fatal cases [24,25]. In additional, in an animal experiment, EV71 was found in the respiratory tract of the rhesus monkeys [19]. Interestingly, some previous studies [26–29] had different opinions. They thought the reason that HFMD patients' lungs were damaged was the neurogenic responses caused by EV71 rather than direct viral invasion, because they could not isolate EV71 virus from lungs and could not observe obvious pathological lesions in lungs. The reasons for those differences were not yet clear. This may because EV71 grew more fastidious and slow than the other enteroviruses, and multiple blind passages were often required for EV71 to be isolated, So cell culture was a time consuming procedure for EV71 isolation, which may decrease the sensitivity [30].

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