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Non-Polio Enterovirus D68 (EV-D68): Implications and Therapeutic Challenges

Review Article

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Abstract

Enterovirus D68 (EV-D68) is being reported as a cause of respiratory illness across USA along with some parts of Canada. Non polio EV-D68 has been associated with respiratory illness followed by acute flaccid paralysis in children which clearly suggests that there should be appropriate screening and treatment of EV-D68 virus. Thus, this review aims to highlight recent research on EV-D68 virus along with its symptoms, diagnosis, possible therapy and associated challenges.

Keywords: Enterovirus; EV-D68; Respiratory illness; Pleconril

Introduction

Enterovirus is positive strand single stranded RNA virus belonging to family picornavirus. The genome of enterovirus is made up of approximately 7500 bases [1]. So far, 71 human serotypes of enterovirus have been established by antibody neutralization tests [2]. The illustration of human enterovirus according to their species and serotypes is given below in Figure 1.

Enteroviruses are the most common microorganisms affecting millions of humans all over the world. These viruses are generally found either in the respiratory tract or stool of the infected person. Although polio is the most common disease caused by enterovirus, now many other diseases are also caused by them. Some of these include nonspecific febrile illness, Pericarditis and/or myocarditis, Acute hemorrhagic conjunctivitis, Herpangina, aseptic meningitis, myocarditis, severe neonatal sepsis-like disease, and acute flaccid paralysis [3].

In this review our focus is on Human Enterovirus D68 (EV-D68). In 1962, EV-D68 was isolated from samples of four children in California who were suffering from bronchiolitis and pneumonia [4].

EV-D68 and human rhinovirus are biologically similar due to its acid-labile nature and also because of association of EV-D68 with respiratory disease, 26 isolates of EV-D68 were reported from 1970 to 2005 in USA [5]. However, outbreaks of EV-D68 have been reported in Japan, Netherlands and some areas of USA for the past three years adding EV-D68 as a new respiratory pathogen [6-8].

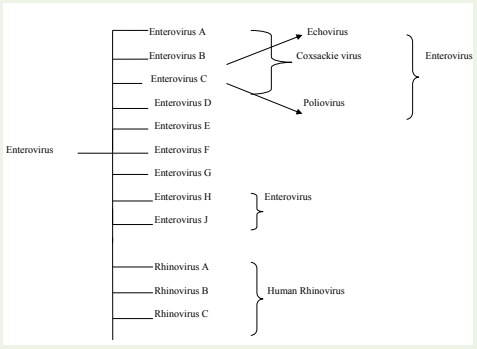

Figure 1: Classification of Enterovirus along with their serotypes.

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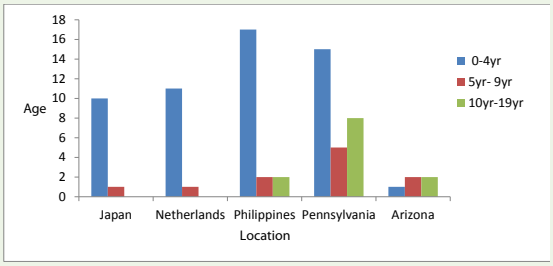

Figure 2: Epidemiology of EV-D68 from 2008-2010.

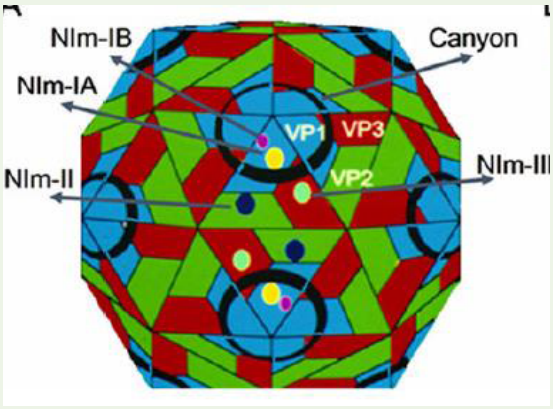

Figure 3: Diagrammatic representation of EV-D68 virus. VP1, VP2, and VP3 are shown in blue green and red respectively [17].

Enterovirus D68 mostly cause respiratory tract infection in children. Structure of Enterovirus consists of icosahedra which is approximately 30nm in diameter. Enteroviruses divide well at 37 °C, under acidic conditions (pH 3.0) although EV-D68 grows optimally at 33 °C and cannot tolerate an acidic environment [9]. Virus can enter the upper respiratory tract of a person either through direct inhalation of aerosolized particles or by transmission of contaminated material through the transfer of infected material from environment. As soon as the virus reaches the upper respiratory tract and attaches itself to the epithelial cells of the mucosal surfaces, it starts to spread.

Recently in USA, outbreak of EV-D68 was observed which was thought to cause respiratory problems. The state public health laboratories in USA asserted that in at least 49 states, 1,153, and in the District of British Columbia, EV-D68 has caused respiratory illness from mid-August 2014 to January 15, 2015. Most of the cases of EV-D68 were found in children who already suffered from asthma or any other respiratory disease [10].

Another case was reported in British Columbia in which a 9 year old patient suffered from acute flaccid paralysis of his left arm followed by respiratory illness and fever. In this case also, EV-D68 was the causative agent which was isolated in nasopharyngeal specimen and intravenous immunoglobulin was used to treat the patient. Still, the patient did not recover the full function of his left arm. This case clearly shows the importance to screen and treat polio and non-polio enteroviruses [11].

Disease Caused by Different Serotypes of Enterovirus

Coxsackie and echovirus: Coxsachie viruses mainly cause hand, mouth and foot diseases. More serious diseases can also be caused by Coxsackie B virus like myocarditis, pericarditis, pancreatitis, and meningitis. Echoviruses can cause many viral infections and are usually found in intestine. Nervous disorders can be caused by this virus. The symptoms of this virus include fever, upper respiratory tract illness, and mild rash [12].

Enterovirus 71: This virus mainly causes mouth, hand, and foot diseases but can also cause central nervous system disease [13]. Isolation and characterization of EV71 was first done in California form neurological cases [14]. It is still not known that how the host response to EV71 infection but increases in mRNAs encoding chemokines, pro-apoptosis proteins, degradation of proteins, and complement proteins have been reported [15].

Poliovirus: Three serotypes of poliovirus have been reported namely, PV1, PV2, and PV3. The difference between these serotypes lies in their caspid proteins. Polio virus affects spinal cord and causes poliomyelitis [16].

Structure of EV-D68: The protein shell of enterovirus also known as capsid is made up of four different viral proteins namely VP1, VP2, VP3 and VP4. The proteins VP1, VP2, and VP3 have "jelly roll" folding and are arranged in the capsid with pseudo T=3 icosahedral symmetry where T is triangulation number. An extended peptide on the inner surface of the capsid is formed by VP4. Enteroviruses also consist of deep surface depression around each of twelve pentameric vertices. This deep surface depression also known as canyon is also said to be the receptor binding site. The external surface of the virus consists of exposed amino acids which can bind to the antibodies. This makes the virus accessible to specific receptor molecule that can bind to the canyon and can easily evade the host's immune response [17].

Most contagious enteroviruses also have a "pocket factor", usually a fatty acid in the VP1 site. Pocket factor also helps in the stabilization of the virus by filling the hydrophobic pocket of VP1. This leads to virus stabilization when it is being transferred to a new host. Although, when the receptor molecule binds to the canyon, the floor is depressed squeezing the binding pocket and throwing out the pocket factor. Thus, when a virus attaches itself to the host cell surface, it initiates uncoating leading to the loss of the genome into the cell's cytosol [17].

When the host cell is infected, the genome gets translated into a single polyprotein. The virus encoding proteases further convert polyprotein to form capsid proteins and nonstructural proteins which help in replication of the virus [18].

Symptoms of EV-D68 infection: Mild symptoms may be including runny nose, sneezing, cough, body and muscle aches. Severe symptoms may be including wheezing and difficulty breathing. EV-D68 causes respiratory illness, the virus can be found in an infected person's respiratory secretions, such as saliva, nasal mucus [19].

Detection: A duplex real-time RT-PCR for rapid screening of

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EV-D68 was developed. The method targeted the 50 non-translated regions (NTR) of the HEV genome at a location generally used for enterovirus detection [19].

Proposed therapy for treatment of EV-D68 caused illness: A flow of EV-D68 cases can be found in past few years and is said to be the cause of respiratory illness in children. There has been spread of EV-D68 in the past few years thought the world [20]. In august 2014 there have occurred thousand of respiratory illness cases in the U.S among children of which 1116 were caused by EV-D68.The virus is the cause of neurological infection as well. Inspite of being big global threat, there is no vaccine or effective antiviral treatment [21]. On October 4, 2014, one death due to enterovirus 68 in New Jersey, USA has been reported. Pleconaril is being tested to treat cases of illness caused by EV-D68 [21]. A caspid binding compound, pleconaril which is an anti-rhinovirus drug is now being used to treat disease caused due to EV-D68. Pleconaril inhibits EV-D68 therefore it is a possible drug that prevents the outbreaks of EV-D68.

It is reported the crystal structures of EV-D68 forms a complex with pleconaril, a capsid binding compound that had been developed as an anti-rhinovirus drugs. The hydrophobic drug binding pocket in viral protein 1(VP1) contained density that is reliable with a fatty acid of on 10 carbon atoms. This density could be displaced by pleconaril. It was also shown that pleconaril inhibits EV-D68 at a half maximal effective concentration (EC50) of 430 nM and might, therefore, is a possible drug candidate to alleviate EV-D68 outbreaks [17].

The anti-EV-D68 activity of 2 capsid binding compounds, pirodavir and BTA-188, that had important anti-rhinovirus activity were compared with pleconaril use plaque reduction assays in HeLa cells. The 0.5 peak effective concentration, EC50, value of those 2 compounds were found to be similar to previous results using cytopathic inhibition assays against EV-D68 [22]. However, pleconaril was found to be more potent against EV-D68 than pirodavir and BTA-188. The suppressive impact of pleconaril is comparable against EV-D68, HRV16, and HRV14 however it is better than against EV-A71. Therefore, pleconaril can be used as a potential drug against intensive clinical cases for treatment of respiratory illness [23]. Moreover, fluorescence-based thermal stability assays indicated that once EV-D68 was incubated with 10 μg/ml or 50 μg/ml pleconaril, 4 °C higher temperatures were needed to unleash the RNA. Therefore pleconaril stabilizes EV-D68 capsids, preventing the virus from uncoating its RNA. Thus, these data suggest that pleconaril can be used as a potential drug to treat illness caused by EV-D68 [17].

Conclusion

EV-D68 is a virus that causes respiratory illness in children. Although the first case of EV-D68 was reported in 1962, recently an outbreak of EV-D68 was reported one of the major cases was of a 9 year old boy in British Columbia, who suffered from partial paralysis due to EV-D68. Apart from this case, there are other cases of respiratory illness along with the association with neurological complications. Another factor which proves that this virus is lethal is that its occurrence has been observed in different countries over a period of time suggesting that this virus can cause worldwide epidemic. Thus, it is necessary to screen EV-D68 in children as well as adults and to find possible drugs for its treatment. Continuous diagnosis of EV-D68 is important to prevent its outbreak. Furthermore, if a link is confirmed between EV-D68 and several other diseases (example: paralysis), finding new therapeutic advances for this disease is need of the hour to prevent mortality caused by EV-D68.

References

1. Li L, He Y, Yang H, Zhu J, Xu X, et al. (2005) Genetic Characteristics of Human enterovirus 71 and coxsackievirus A16 circulating from 1999 to 2004 in Shenzhen, People's Republic of China. J Clin Microbiol 43: 3835-3839.
2. Oberste MS, Maher K, Kilpatrick DR, Pallansch MA (1999) Molecular evolution of the human enteroviruses: correlation of serotype with VP1 sequence and application to picornavirus classification. J Virol 73: 1941-1948.
3. Non-Polio Enterovirus Infections. CDC. 8 September 2014. Retrieved 9 September 2014.
4. Schieble JH, Fox VL, Lennette EH (1967) A probable new human picornavirus associated with respiratory diseases. Am J Epidemiol 85: 297-310.
5. Khetsuriani N, Lamonte-Fowlkes A, Oberst S, Pallansch MA, Centers for Disease Control and Prevention (2006) Enterovirus surveillance-United States, 1970–2005. MMWR Surveill Summ 55: 1-20.
6. Jacobson LM, Redd JT, Schneider E, Lu X, Chern SW, et al. (2012) Outbreak of lower respiratory tract illness associated with human enterovirus 68 among American Indian children. Pediatr Infect Dis J 31: 309-312.
7. Hasegawa S, Hirano R, Okamoto-Nakagawa R, Ichiyama T, Shirabe K (2011) Enterovirus 68 infection in children with asthma attacks: virus-induced asthma in Japanese children. Allergy 66: 1618-1620.
8. Imamura T, Fuji N, Suzuki A, Tamaki R, Saito M, et al. (2011) Enterovirus 68 among children with severe acute respiratory infection, the Philippines. Emerg Infect Dis 17: 1430-1435.
9. Oberste MS, Maher K, Schnurr D, Flemister MR, Lovchik JC, et al. (2004) Enterovirus 68 is associated with respiratory illness and shares biological features with both the enteroviruses and the rhinoviruses. J Gen Virol 85: 2577-2584.
10. Report from Centers for Disease Control and Prevention, USA.
11. Sherwood MD, Gantt S, Connolly M, Dobson S (2014) Acute flaccid paralysis in a child infected with enterovirus D68: A case report. BCMJ 56: 495-498.
12. Santti J, Heli H, Leena K, Timo H (2000) Molecular epidemiology and evolution of coxsackievirus A9. J Gen Virol 81: 1361-1372.
13. Lin TY, Chu C, Chiu CH (2002) Lactoferrin inhibits enterovirus 71 infection of human embryonal rhabdomyosarcoma cells in vitro. J Infect Dis 186: 1161-4.
14. Wang SY, Lin CL, Sun HC, Chen HY (1999) Laboratory Investigation of a Suspected Enterovirus 71 Outbreak in central Taiwan. Epidemiol Bull 215-219.
15. Shih SR, Stollar V, Lin JY, Chang SC, Chen GW, et al. (2004) Identification of genes involved in the host response to enterovirus 71 infection. J Neurovirol 10: 293-304.
16. Paul JR (1971) A History of Poliomyelitis (Yale studies in the history of science and medicine). New Haven, Conn: Yale University Press.
17. Liu Y, Sheng J, Fokine A, Meng G, Shin WH, et al. (2015) Structure and inhibition of EV-D68, a virus that causes respiratory illness in children. Science 347: 71-74.
18. Merkle I, van Ooij MJ, van Kuppeveld FJ, Glaudemans DH, Galama JM, et al. (2002) Biological significance of a human enterovirus B-Specific RNA element in the 3′ Nontranslated region. J Virol 76: 9900-9909.
19. Bragstad K, Jakobsen K, Rojahn AE, Skram MK, Vainio K, et al. (2015) High frequency of enterovirus D68 in children hospitalised with respiratory illness in Norway, autumn 2014. Influenza Other Respir Viruses 9: 59-63.

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20. Tokarz R, Firth C, Madhi SA, Howie SRC, Wu W, et al. (2012) Worldwide emergence of multiple clades of enterovirus 68. J Gen Virol 93: 1952-1958.

21. Kreuter JD, Barnes A, McCarthy JE, Schwartzman JD, Oberste MS, et al. (2011) A fatal central nervous system enterovirus 68 infection. Arch Pathol Lab Med 135: 793-6.

22. Barnard DL, Hubbard VD, Smee DF, Sidwell RW, Watson KGW, et al. (2004) In vitro activity of expanded-spectrum pyridazinyl oxime ethers related to pirodavir: novel capsid-binding inhibitors with potent antipicornavirus activity. Antimicrob Agents Chemother 48: 1766-1772.

23. Hayden FG, Herrington DT, Coats TL, Kim K, Cooper EC, et al. (2003) Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials. Clin Infect Dis 36: 1523-32.

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