Editorial
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Mixed Respiratory Viral Infections in Children with Adenoviral Infections

Jin Lee

Department of Pediatrics, Hanil General Hospital, Seoul, Korea

Human adenoviruses are a common cause of diseases. While epidemic diseases caused by adenoviruses were observed throughout the first half of the 20th century, the viruses were first noted in explant cultures of human adenoidal surgical specimens in 1953; this finding, plus the observation of their apparent general affinity for lymphatic tissue, led to naming designation [1, 2].

More than 50 serotypes grouped into eight species have been defined according to antigenic variability in the surface proteins of the virion. The species differ in their tissue tropism and target organs, causing distinct clinical infections. The most prevalent types in recent surveillance studies are human adenovirus types 3, 2, 1, and 5 [3]. Adenoviral infections cause a wide spectrum of diseases. Adenoviral infections account for 2 to 5% of all respiratory illnesses, and are estimated to be responsible for 2 to 35% of respiratory viral illnesses in children [2]. Adenoviruses spread by respiratory and fecal-oral routes, and are frequently isolated from the conjunctiva, throat, and stool.

Adenoviral infections are diagnosed by isolation of virus in tissue culture, direct antigen detection assay, or by DNA polymerase chain reaction (PCR). Molecular techniques, such as PCR, offer rapid, sensitive, and specific diagnosis of adenoviral infections and are becoming the gold standard for diagnosis. A real-time PCR assay for the qualitative detection of all 57 adenovirus serotypes with high sensitivity and specificity in a variety of clinical samples is also available. Moreover, the expanded use of direct fluorescent assays and multiplex PCR assay enables identification of multiple co-infecting viruses and bacteria. Investigators are discovering the common prevalence of adenovirus coinfections with multiple serotypes, other viruses and bacteria [2].

Respiratory viral co-infections, defined as the presence of more than one viral pathogen in the same sample are detected in up to 30% of children with acute respiratory tract infections [4]. The clinical significance and the mechanisms of disease virulence in respiratory viral coinfections remain uncertain. Recent systematic reviews and meta-analyses revealed no significant differences between children with single respiratory virus infection and those with viral-viral coinfection with respect to the length of hospital stay, admission to the intensive care unit, need for mechanical ventilation, oxygen require-

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Corresponding Author : Jin Lee, MD
Department of Pediatrics, Hanil General Hospital, 308 Uicheon-ro, Dobong-gu, Seoul 01450, Korea
Tel: +82-2-901-3029, Fax: +82-2-901-3819
E-mail: pedleejin@naver.com

ments and death [5, 6]. With increasing identification of multiple viruses as etiologic microorganisms, the clinical role of interactions between specific viruses remains to be determined.

Reports on the clinical impact of viral coinfection in patients with adenovirus infections are sparse. Some investigators reported a lack of association between viral coinfections and clinical severity in children with adenoviral infections [7]. In another retrospective study in Korea, coinfections with other respiratory viruses were frequent in children with adenoviral infections under 2 years of age [8].

In a single-center retrospective study in Seoul, Korea, Lee et al. [9] assessed 105 hospitalized children diagnosed with adenovirus infections in order to determine the clinical impact of viral coinfection in children with adenovirus infections. Coinfection with other viruses was identified in 30.5% of children, most frequently rhinovirus (46.9%), and respiratory syncytial virus (21.9%). However, the researchers did not identify the types of adenoviruses. Respiratory viral coinfection with adenoviruses occurred more frequently in children less than 24 months of age compared with older children. However, coinfection did not lead to mortality, and the duration of fever and hospitalization did not differ significantly between the adenovirus only and coinfection groups. As the authors mentioned, most other studies reported a higher incidence of respiratory viral coinfection in younger age groups than in older ones.

The clinical significance of coinfection in children with adenovirus infections remains difficult to establish from retrospective observational data. Identifying adenovirus serotypes is important in order to correlate the wide spectrum of clinical disease or symptoms with specific adenovirus serotypes as well as interactions with other viruses in cases of coinfection. Patient history of attendance at daycare centers, number of siblings and socioeconomic status may influence the acquisition of multiple viruses and severity. The interaction between specific viruses (*e.g.,* adenovirus vs., rhinovirus and, adenovirus vs. respiratory syncytial virus) and identification of the independent effects of each virus increase understanding regarding the mechanisms of disease in viral coinfection.

Respiratory virus infection induces damage to the epithelial mucosa of airways, Eustachian tube, and middle ear, exposing surface elements to which bacteria can adhere [6]. In addition, respiratory viral infections predispose patients to secondary bacterial pulmonary infections [4]. The significance of respiratory viral-bacterial coinfection in children is rarely evaluated. The overall prognosis of adenoviral infection is excellent but the prognosis in the very young and in immunocompromised patients may be poor. Secondary bacterial complications, if not properly treated, can also result in prolongation of illness and permanent sequelae. Secondary bacterial pneumonias do not appear to be as common following adenovirus infection as they are following influenza infection, however data are scarce regarding this issue [3].

With the increased sensitivity of molecular assays, the rate of virus detection in asymptomatic children is also high (up to 68%), as are coinfection rates in symptomatic children (up to 43%); justified concerns regarding causality have also been raised [10]. Shedding of dead and potentially non-pathogenic viruses may be detected, which are difficult to distinguish from true pathogens. Clinical correlations and other laboratory findings should also be considered when interpreting positive PCR results.

The use of multiplex PCR methods, to identify viral-viral as well as viral-bacterial coinfections in future studies may clarify the clinical implication of polymicrobial respiratory infections; certain pairings of pathogens (virus-virus or virus-bacteria) may be more clinically relevant than others.

In conclusion, adenovirus is a common causative pathogen in children. Although more than 50 serotypes cause a wide range of disease, multiplex PCR techniques allow identification of each serotype. Other viruses are also found in patients with adenoviral infection; however the significance of viral coinfection with adenovirus in pediatric patients is poorly understood. Younger age (less than 24 months) has been associated with coinfection. However, the overall prognosis and disease severity of viral coinfection with adenovirus is not significantly different from that of adenovirus-only infections. Many microbial agents are more frequently detected using current molecular diagnostic tools than in the usual clinical settings. A prospective, multi-center study of a large numbers of subjects observed over a long period of time is necessary to evaluate the relationship between multiple viral coinfections and single viral infections including adenoviruses.

Conflicts of Interest

No conflicts of interest.

ORCID

Jin Lee http://orcid.org/0000-0002-6039-2224

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