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ORIGINAL ARTICLE

Risk factor analysis and molecular epidemiology of respiratory adenovirus infections among children in northern Taiwan, 2009–2013

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Abstract *Background/Purpose:* Respiratory infections caused by human adenoviruses (HAdV) are worldwide, and have significantly increased recently in Taiwan. This study aimed to clarify the molecular epidemiology and risk factors of HAdV severe infections and pneumonia among Taiwanese children.
Methods: Patients with HAdV infections and hospitalized in a medical center between 2009 and 2013 were divided into severe or nonsevere HAdV infections based on whether or not they received intensive care. HAdV pneumonia was identified for comparison. The HAdV genotype was determined by sequencing the partial hexon and fiber genes. The nucleotide sequences were compared by phylogenetic analysis.
Results: The 176 patients (97 boys, 79 girls) had a median age of 3.7 years. The HAdV infections circulated year-round. HAdV B3 (54.5%) was the most common genotype, followed by HAdV C2

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(21%), HAdV E4 (8%), and HAdV B7 (6.8%). Thirty-two patients needed intensive care. In multivariate analysis, the risk factors for severe HAdV infections were underlying neurologic diseases [odds ratio (OR): 164.9; $p < 0.001$], prematurity (OR: 10.9; $p = 0.042$), and HAdV B7 (OR: 39.5; $p = 0.011$). Twenty-nine patients had HAdV pneumonia. Patients with underlying neurologic diseases (OR 76.8; $p < 0.001$), airway anomaly (OR 15.1; $p = 0.033$), chronic lung diseases (OR 12.5; $p = 0.047$), weight $< 3^{rd}$ percentile (OR 5.5; $p = 0.027$), and HAdV B7 (OR 4.2; $p = 0.002$) had higher incidences of pneumonia. Four with underlying neurologic diseases died of acute respiratory distress syndrome.

Conclusion: HAdV infections circulate all year-round. HAdV B7 is strongly related to severe infections and pneumonia. Underlying neurologic diseases and prematurity are risk factors for severe HAdV infections.

Introduction

Human adenoviruses (HAdV) are nonenveloped DNA viruses and are common causative pathogens of acute respiratory infections. In the past few years, there has been a significant increase in the incidence of HAdV infections in Taiwan.[1,2] It may cause a wide variety of clinical manifestations, from the common cold, tonsillitis, pharyngoconjunctival fever, acute otitis media, and gastroenteritis, to life-threatening pneumonia, myocarditis, and meningoencephalitis.[3–5] Some studies have reported an association between HAdV in childhood and outcomes.

The HAdV serotypes and characteristics of children have been shown to play an important role in outcome. Children aged 1—2 years are at higher risk of lower respiratory tract infections than those of other age groups.[6] Life-threatening HAdV infections are reported in younger children, immunocompromised patients, those with underlying chronic diseases, and previously healthy children.[7–9] Greater knowledge about differences in virulence and organ tropism among the HAdV serotypes increase the medical value of HAdV classification.[10]

In general, HAdV species B, C, and E (HAdV-B, -C, and -E) cause respiratory infections. They are distributed globally and occur throughout the year, crossing all age groups. HAdV-B3 has been common in Taiwan in the previous years.[11] A prior report shows that HAdV serotype 3 causes the most HAdV infections in the autumn and winter of 1999—2000.[12] Certain serotypes are associated with particular clinical features and severe illness and HAdV serotypes 3, 5, 7, and 21 have caused death after severe infections. Among these serotypes, serotypes 3 and 7 have a higher risk of causing severe respiratory illness.[1,8,13,14]

However, studies on risk factors of severe HAdV infections and molecular epidemiology of HAdV are limited in Taiwan. The aim of this study was to determine the molecular epidemiology of HAdV, its clinical presentations, and the risk factors of severe HAdV infections among Taiwanese children.

Methods

Ethics statement

The Ethics Committee of MacKay Memorial Hospital, Taipei, Taiwan, R.O.C. approved the study protocol (Institutional Review Board number 14MMHIS 162).

Patient inclusion

This study enrolled 176 children aged 18 years or younger with positive HAdV cultures and admitted to the Pediatric Department of MacKay Memorial Hospital, a tertiary medical center, between January 2009 and December 2013. The medical charts were reviewed and the demographic data, clinical features, laboratory results, chest X-ray, underlying diseases, clinical diagnosis, and outcomes were analyzed.

Viral culture and adenovirus genotyping

Virus cultures were performed via throat swabs with sterile cotton buds and nasopharyngeal aspirates (NPA) from all participants within 48 hours of admission. The specimens were preserved in standard transport media under refrigeration and transported to the Department of Clinical Virology and Microbiology Laboratory of MacKay Memorial Hospital for virus culture.[15] The viral stocks consisted of only supernatant and stored at −80°C immediately after harvest until use.

Nucleic acid extraction was performed using a High Pure Viral Nucleic Acid kit (Roche, Basel, Switzerland) according to the manufacturers' instructions. Partial hexon gene was amplified by polymerase chain reaction (PCR), which was set according to a previous study.[16]

The PCR assay was conducted using the SapphireAmp Fast PCR Master Mix (TaKaRa Inc., Shiga, Japan). Amplification was performed in a GeneAmp PCR System 9700 thermocycler (Applied Biosystems Inc., Carlsbad, CA, USA) with the following parameters: 94°C for 1 minute followed by 40 cycles of 20 seconds at 98°C, 30 seconds at 60°C, 1

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