Human adenovirus among hospitalized children with respiratory tract infections in Beijing, China, 2017–2018

Li-hong Yao†, Chao Wang†, Tian-li Wei‡, Hao Wang, Fen-lian Ma* and Li-shu Zheng*

Abstract

Background: Human adenoviruses (HAdVs) cause a wide range of diseases. However, the genotype diversity and epidemiological information relating to HAdVs among hospitalized children with respiratory tract infections (RTIs) is limited. Here, we describe the epidemiology and genotype distribution of HAdVs associated with RTIs in Beijing, China.

Methods: Nasopharyngeal aspirates (NPA) were collected from hospitalized children with RTIs from April 2017 to March 2018. HAdVs were detected by a TaqMan-based quantitative real-time polymerase chain reaction (qPCR) assay, and the hexon gene was used for phylogenetic analysis. Epidemiological data were analyzed using statistical product and service solutions (SPSS) 21.0 software.

Results: HAdV was detected in 72 (5.64%) of the 1276 NPA specimens, with most (86.11%, 62/72) HAdV-positives cases detected among children < 6 years of age. HAdV-B3 (56.06%, 37/66) and HAdV-C2 (19.70%, 13/66) were the most frequent. Of the 72 HAdV-infected cases, 27 (37.50%) were co-infected with other respiratory viruses, most commonly parainfluenza virus (12.50%, 9/72) and rhinovirus (9.72%, 7/72). The log number of viral load ranged from 3.30 to 9.14 copies per mL of NPA, with no significant difference between the HAdV mono- and co-infection groups. The main clinical symptoms in the HAdV-infected patients were fever and cough, and 62 (86.11%, 62/72) were diagnosed with pneumonia. Additionally, HAdVs were detected throughout the year with a higher prevalence in summer.

Conclusions: HAdV prevalence is related to age and season. HAdV-B and HAdV-C circulated simultaneously among the hospitalized children with RTIs in Beijing, and HAdV-B type 3 and HAdV-C type 2 were the most frequent. Keywords: Human adenovirus, Respiratory tract infection, Epidemiology

Background

First discovered in 1953 by Rowe et al., human adenoviruses (HAdVs) are non-enveloped, double-stranded DNA viruses belonging to the Mastadenovirus genus (Adenoviridae family). They are common pathogens in children and cause a variety of diseases [1]. HAdV accounts for at least 5 to 10% of pediatric and 1 to 7% of adult respiratory tract infections (RTIs) [2]. There are currently seven different HAdV species (A to G), some of which specifically attack the conjunctiva (species D), the upper and lower respiratory tracts (species B, C and E), and the gastrointestinal tract (species F and G) [3]. Of the 90 AdV serotypes, 55 are known to cause human diseases, with AdV3, 4, 7 and 14 being the most common types to cause respiratory disease outbreaks [4]. HAdV has caused respiratory tract adenovirus outbreaks in Jiangsu and Taiwan provinces of China, as well as in Korea, Singapore and Malaysia [5–7]. Such infections have been estimated to cause 2–5% of RTIs overall and 4–10% of all pneumonias in City of Bethlehem [8]. Although HAdVs are associated with mild to moderate disease in most cases, life threatening disease can occur in some patients, particularly if they are immunocompromised.
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the relationship between vomiting and HAdV types was statistically analyzed by Fisher’s exact probability, with statistical significance set at $P < 0.05$. Vector NTI 11.0 software was used for sequence alignment and Mega 5.0 software for phylogenetic analysis. Epidemiological data were analyzed using statistical product and service solutions (SPSS) 21.0 software.

**Results**

**Characteristics of the inpatient children**

In total, 1276 NPA specimens were obtained from 1276 children with RTIs at Beijing Friendship Hospital, among which 674 (52.82%) were male and 602 (47.18%) were female (Table 1), all children survived, and the age range was from 1 day to 14 years of age with a median age of 3 years. From them, 897 (70.30%) patients were younger than 5 years old.

**Epidemiology of HAdV**

HAdVs were detected in 5.64% (72/1276) of the hospitalized children. As shown in Table 1, among the 72 HAdV-positive patients, 45 (62.50%) were male and 27 (37.50%) were female (a male/female ratio of 1.6:1). No significant difference was observed in males and females in the HAdV-positive cases ($P = 0.090$). HAdV was detected among hospitalized children (< 14 years) with RTIs at Beijing Friendship Hospital between April 2017 and March 2018, and there were significant differences in HAdV detection rates among different age groups ($P = 0.008$). Children under 6 years old accounted for 86.11% (62/72) of the infections. The HAdV detection rate peaked in the > 5 to ≤ 6 years age group (12.79%, 11/86), while those in the ≤ 1 years old group had a relatively low detection rate of 3.18% (10/314). HAdV was detected in every month throughout the study period from April 2017 to March 2018, peaking in summer. The HAdVs detection frequencies were 5.60% (18/321), 9.52% (30/315), 3.31% (10/302) and 4.14% (14/338) ($\chi^2 = 16.06, P = 0.001$) in the spring, summer, autumn and winter months, respectively. Additionally, the HAdV detection rate peaked at 10.91% (12/110) in August 2017 (Fig. 1).

**Coinfections with other respiratory viruses**

Of the 72 HAdV-infected cases, 27 (37.50%) comprised co-infections with other respiratory viruses including 21 (77.78%, 21/27) with one other virus, 3 (11.11%, 3/27) with two other viruses, 2 (7.41%, 2/27) with three other viruses and 1 (3.70%, 1/27) with four other viruses. The most frequently identified mixed infection was PIV (12.50%, 9/72) and HRV (9.70%, 7/72), as shown in Table 2. Among the HAdV-positive specimens, the log number of HAdV genome copies ranged from 3.30 to 9.14 copies per mL of NPA, as determined by the qPCR assay measurements (Fig. 2). The log number for the HAdV genome copies was 6.14 ± 1.52 copies/mL of NPA in the children infected with HAdV only, which is slightly higher than the 5.70 ± 1.39 copies/mL of NPA from those co-infected with HAdV and other respiratory viruses; there was, however, no significant difference in the viral loads between the HAdV mono- and co-infections ($P = 0.220$).

**Clinical characteristics of the HAdV infections**

Sixty-two of the patients (86.11%, 62/72) from the 72 HAdV-positive cases were diagnosed with pneumonia, including 46 with bronchopneumonia, 4 with asthmatic bronchitis, 3 with refractory bronchopneumonia, 8 with pneumonia (3 with mycoplasma pneumonia, 3 with bacterial pneumonia and 2 with viral pneumonia) and 1 with refractory pneumonia. Viral pneumonia and bacterial pneumonia accounts for 3.23% (2/62) and 4.84% (3/62) of the pneumonia, respectively. In addition, the remaining 10 cases were diagnosed with acute tonsillitis (5), acute upper respiratory infection (2), acute bronchitis (2), as well as 1

| Variable | Number of children | Number of children positive for HAdV | Percentage children positive for HAdV (%) | $P$ value |
|----------|--------------------|--------------------------------------|----------------------------------------|-----------|
| Age (years) |                     |                                      |                                        | 0.008     |
| ≤ 1      | 314                | 10                                   | 3.18                                   |           |
| > 1 to ≤2| 140                | 9                                    | 6.43                                   |           |
| > 2 to ≤3| 109                | 10                                   | 9.17                                   |           |
| > 3 to ≤4| 193                | 13                                   | 6.73                                   |           |
| > 4 to ≤5| 141                | 9                                    | 6.38                                   |           |
| > 5 to ≤6| 86                 | 11                                   | 12.7                                   |           |
| > 6 to ≤14| 293               | 10                                   | 3.41                                   |           |
| Gender   |                     |                                      |                                        | 0.090     |
| Male     | 674                | 45                                   | 6.67                                   |           |
| Female   | 602                | 27                                   | 4.48                                   |           |
| Total    | 1276               | 72                                   | 5.64                                   |           |
with Epstein-Barr virus-associated infectious mononucleosis. The main clinical signs in the HAdV-positive patients were fever (97.22%, 70/72) and cough (75%, 54/72), while the other clinical presentation were vomiting (18.06%, 13/72), gasping (15.28%, 11/72), diarrhea (4.17%, 3/72) and angina (5.56%, 4/72). Furthermore, vomiting didn’t associate with specific HAdV types by Fisher’s exact probability (P = 0.069). In this study, of the 72 HAdV-positive children with RTIs, 4 (5.56%, 4/72) had asthma, the other 68 had no pre-existing chronic conditions.

**HAdV genotyping and phylogenetic analysis**

Basing on the 956-bp fragment of the hexon gene amplified by nested-PCR, 66 HAdV-positive samples were sequenced and successfully genotyped. The phylogenetic analyses indicated that 41 cases belonged to species B (HAdV-B3, HAdV-B7, and HAdV-B35) and 25 belonged to species C (HAdV-C2, HAdV-C1, and HAdV-C5) (Table 3). Six of the samples failed to be typed. The above-mentioned results indicate that species B and C (at least 6 HAdV genotypes) circulated simultaneously in Beijing, and that HAdV-B3 was the most prevalent genotype, followed by HAdV-C2 (Fig. 3).

**Discussion**

The present study was carried out between April 2017 and March 2018 among hospitalized children with RTIs in Beijing, China. Herein, we describe (i) the prevalence of HAdVs in hospitalized children with RTIs presenting at Beijing Friendship Hospital during a one-year period; (ii) the clinical spectrum of the HAdV-positive RTI patients; (iii) the viral co-pathogens present in the HAdV infections; and (iv) the genetic diversity of the HAdVs.

The clinical characteristics of the RTIs caused by HAdV are very similar to those of influenza, PIV and other respiratory tract pathogens, making it difficult to clinically diagnose this type of infection. Therefore, effective diagnostic methods are needed for rapid identification and genotyping of HAdV. The qPCR assay used herein was established to detect and quantify HAdV. A total of 1276 NPA specimens were screened for the presence of HAdV and 72 specimens (5.64%, 72/1276) were confirmed to be positive for HAdV, which is consistent with prior reports (1.70–13.90%) [16–18]. The detection rate for HAdV varies from region to region in China, and the rate for hospitalized children with acute lower RTIs in Zhejiang province from 2006 to 2012 was 0.63, and 2.24% in Shenzhen city from 2012 to 2015 [19, 20]. However, it is worth mentionin that such discrepant HAdV detection rates can be caused by methodological differences, the number of patients tested, the periods during which the samples are collected, and even a study’s duration.

**Table 2** Co-detection of HAdV and other respiratory viruses

| Coinfection | Virus composition       | Number of cases |
|-------------|-------------------------|-----------------|
| 2 Virus (N = 21) | HAdV+HRV               | 7               |
|             | HAdV+PIV                | 5               |
|             | HAdV+HCoV               | 3               |
|             | HAdV+RSV                | 2               |
|             | HAdV+HMPV               | 2               |
|             | HAdV+WUPyV              | 1               |
| 3 Viruses (N = 3) | HAdV+PIV + RSV       | 2               |
|             | HAdV+HCoV+FluA          | 1               |
| 4 Viruses (N = 2) | HAdV+PIV + HCoV+HMPV   | 1               |
|             | HAdV+RSV + HBoV+WUPyV  | 1               |
| 5 Viruses (N = 1) | HAdV+PIV + RSV + HMPV+WUPyV | 1               |
Previous studies have shown that HAdV detection rates are positively correlated with the monthly mean temperature and sunshine duration, and negatively correlated with wind speed; in fact, the higher the air temperature, the higher the detection rate [21]. Our study also revealed that HAdV infections occurred throughout the year with the highest prevalence in the summer (9.52%, Jun to Aug), peaking in August (10.91%), which is similar to what has been found in Tianjin, a northern Chinese city, where HAdV infections are concentrated during the summer [22]. However, this finding is discordant with other studies that have reported seasonal peaks for HAdV infections in spring in Northern China and Mexico [23, 24].

We found that the HAdV infections occurred predominantly in children under 6 years of age (86.11%), demonstrating that HAdV is an important pediatric pathogen. Previous studies drew identical conclusions that most children become infected by HAdV at an early age [18, 25, 26]. HAdVs can be easily transmitted through fomites contaminated with infectious body fluids. In our study, the HAdV detection rate (3.18%) was lowest among children under 1 year of age, and the reasons need to be further explored.

Many studies have reported that the most common HAdV species causing RTIs in children are B (B3, B7, B21), C (C1, C2, C5, C6) and E (E4) worldwide [27, 28]. HAdV 2, 3 and 7 are the most prevalent species and are associated with severe pneumonia in China [29, 30]. In the present study, a total of 66 samples were identified and phylogenetically analyzed based on the hexon gene sequence, which revealed six HAdV genotypes and showed that HAdV species B and C were the most prevalent, accounting for 62.12 and 37.88% of isolates, respectively. Similarly to what has been found in Asia by other authors, HAdV-B3 was the most common type (56.06%, 37/66) followed by HAdV-C2 (19.70%, 13/66) and C1 (10.61%, 7/66). HAdV-B3 has been identified as the causative pathogen for severe acute respiratory illness outbreaks in Korea [31], Brazil [32] and Taiwan [33], and it was the main type of respiratory HAdV infections from 1981 to 2002.
Moreover, HAdV-B3 was the pathogen causing epidemic respiratory disease outbreaks in Europe, America, and Oceania. Last, HAdV-B3 is known to cause a characteristic syndrome in older children and adults, as manifested by acute pharyngo-conjunctival fever, especially after contact with summer camps and swimming pools [34]. HAdV-C1 and HAdV-C2 have been frequently reported to cause endemic, sporadic and epidemics cases [35, 36].

In the present study, the most common diagnosis (86.11%) in the HAdV-positive cases was pneumonia, with the common signs and symptoms of fever and cough, which is consistent with previous reports [16–18]. HAdV infection is often accompanied by other virus infections. Our study showed that PIV (12.50%, 9/72) was the major co-infecting pathogen identified followed by HRV (9.70%, 7/72). Although the viral load from children mono-infected with HAdV was slightly higher than those co-infected with HAdV and other respiratory viruses, no significant difference was seen between the two groups. The severity of HAdV infection varies according to age, socioeconomic status, environmental status and, above all, the immunological characteristics of the patient. Therefore, the etiological significance of co-infections with HAdV and other respiratory viruses and its association with disease severity require further study. It was reported HAdV can cause more severe illness in immunocompromised patients, so it would be very valuable to know about pre-existing conditions in HAdV-positive children. Except for 4 cases of asthma, there were no other comorbidities in our study. Taken together, our results provide a foundation for further clarification of the role played by HAdVs in RTIs and for

Fig. 3 Phylogenetic analysis of nucleic acid sequences of HAdV hexon gene (956-bp) compared with reference strains
defining the clinical and public health significance of HAdV infections.

Conclusions
This 1-year study documented the prevalence, age distribution, seasonality and molecular epidemiology of HAdV infections among children hospitalized with RTIs at Beijing Friendship Hospital. Our results reveal recent changes in the trends for circulating HAdV genotypes linked to RTIs in Beijing, China, which should be of value for improving the diagnosis of HAdV-related diseases and for developing new detection, treatment and prevention strategies for broad application in clinical laboratories. However, only a 956-bp region of hexon gene was sequenced for genetic analysis in the present study. Therefore, a future full-length genome analysis would help us to understand the extent of genetic variation and any potential recombination that has occurred in the strains referred to above.

Abbreviations
CT: Cycle threshold; FLuA: Influenza A virus; FLuB: Influenza B virus; HAdVs: Human adenoviruses; HBoV: Human bocavirus; HCoV: Human coronavirus; HMPV: Human metapneumovirus; HRV: Human rhinovirus; Mega: molecular evolutionary genetics analysis; NPA: Nasopharyngeal aspirate; PIVs: Parainfluenza viruses; qPCR: quantitative real-time polymerase chain reaction; RTIs: Respiratory tract infections; SPSS: Statistical product and service solutions; WUPyV: Wu polyomavirus

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Authors’ contributions
LY, FM and CW performed the experiments. FM and LZ conceived and designed the experiments. FM, TW, HW and LZ analyzed the data. CW, HW and TW performed the experiments. FM and LZ conceived and designed the experiments. FM and LZ wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets supporting the conclusions of this article are included within the article.

Ethics approval and consent to participate
The project was approved by the Ethical Committee of National Institute for Viral Disease Control and Prevention, China CDC, and the committee’s reference number is 012, ND/CDC 2018.

Consent for publication
Written informed consent for specimen collection, testing and publication was obtained from the patients’ parents or guardians.

Competing interests
The authors declare that they have no competing interests.

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