Human adenovirus infection of 53 children in Jilin Province of China: the clinical and bronchoscopic features

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Research article

Keywords: Human Adenovirus, pneumonia, electronic bronchoscope, Children

Posted Date: July 19th, 2019

DOI: <https://doi.org/10.21203/rs.2.11736/v1>

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Abstract

Abstract Background: Human adenoviruses (HAdV) has many kinds of serotypes, of which type 7 can cause severe respiratory disease, especially pneumonia. From Oct 1st to Jan 31st a little outbreak of this type occurred in Jilin province of China and led to quite severe pneumonia, therefore we did this retrospective study to summarize the clinical and bronchoscopic features in order to help pediatric physicians get better view of the infection. **Methods:** Nasopharyngeal swabs or bronchoalveolar lavage fluid (BALF) were collected from pediatric patients who were diagnosed with pneumonia in our department of the First hospital of Jilin University from Oct 1st 2018 to Jan 31st 2019. Then use immunofluorescence method (detect the nasopharyngeal swabs) or the next-generation sequencing technology (detect the BALF) to clarify the pathogen. **Results:** 53 children were confirmed to be infected with the HAdV, the mean age of infected children was 39.5(39.5±25.09) months, 56.6% were less than 36 months. The ratio rate between male and female was 1.3:1. Co-infection was quite common (75%), and happened in older group($p=.018$). Bronchoscope was performed on 37 children, 45.9%($n=17$) had micro-sputum-bolt in the small distal airway or in the BALF. With the help of the next-generation sequence technology, 11 were confirmed infected with HAdV-7. We followed up the patients for 6 months, 12 by CT and 41 by telephone call. In the CT follow-up group, 8 had “Mosaic sign” on lung CT, and 4 shows mild uneven ventilation. In telephone follow-up group 31 recovered well and had no symptoms, 10 had cough and tachypnea after moderate level of daily activities. **Conclusion:** A) Compared with previous data in our hospital, in the winter this year, a little outbreak happened in Jilin province of China. B) We infer that HAdV-7 may be the prevalent strain. C) Before we get accurate etiology diagnosis, combining with the clinical symptoms, accessory results, the micro-sputum-bolt seen in the BALF when doing the electronic bronchoscope can give us some hints of HAdV infection.

Background

Human adenovirus (HAdV) are non-enveloped viruses containing double-stranded linear DNA [1], which were first isolated in 1953 as respiratory pathogens[2, 3]. They belong to the family *Adenoviridae*, genus *Mastadenovirus* and are categorized into seven species (A-G) according to their biophysical, biochemical, and genetic characteristics[4]. To date, 90 genotypes have been cognized[5]. Among these species, species B (HAdV-B3 and HAdV-B7) are usually associated with respiratory diseases[6]. Moreover, respiratory infections due to HAdV cause significant morbidity and mortality, with case fatality rates as high as 12%[7].

Many outbreaks of acute respiratory infection caused by HAdV have been reported during the last decade in many countries including China[8-17]. Such outbreaks were also reported in the community and in military and police camps between 2011 and 2013, in

Taiwan, Singapore, China and Malaysia [18-22]. From Oct 1st 2018 to Jan 31st 2019 a little outbreak of HAdV happened in Jilin province of China. As the severity and prevalence of such kind of infection, we did the retrospective study.

Methods

Study Design

This is a retrospective study, and focus on the inpatient patients who got to our department from Oct 1st to Jan 31st. The following Information were collected: A) Demographic data; B) Clinical data; c) Images of lung CT and electronic bronchoscope.

Inclusion criteria

Children who were under 16-year-old diagnosed with pneumonia from Oct 1st 2018 to Jan 31st 2019 in our department meeting the following conditions would be included: A) Nasopharyngeal swabs results were HadV positive; B) Using the-generation-sequence technology to detect the BALF and confirmed the HadV infection.

Virus Detection

1. Direct immunofluorescence (DIF): Nasopharyngeal swabs, collecting from the patients after the admission, were sent to the lab and use Seven Respiratory Viruses Kit (Diagnostic Hybrids America) to detect. The kit can detect following viruses: influenza A virus, influenza B virus, Parainfluenza virus type1,2and3, respiratory syncytial virus (RSV) and Human Adenovirus (HAdV). In our study, 42 swabs were tested by this method.
2. The next-generation-sequence technology (NGS): For those we highly suspect to be co-infected (such as long duration of fever, high temperature and general status was bad), and the patients' parents agreed to do the examination used the NGS to detect the pathogens. We reserved the BALF and ask a company ("BGI" the

company's name) to test the sample. The technology can detect thousands of pathogens including bacteria, fungus, virus and other untypical pathogens. Above all we can get the genotype of the virus, which make up for the defect of the DIF.

In the study, 11 BALFs were tested by this method.

Statistical method

The data collected were analyzed by SPSS 22.0 version. Continuous variables were presented as the mean values and standard deviations (SDs), categorical variables were presented as percentages. Continuous data were analyzed by two-sided Student's t-test, when ensuring the data were normally distributed or using a two-sided Wilcoxon's rank-sum test if the data were non-normal. For categorical data, group comparisons were performed by using a contingency table analysis with a χ^2 or Fisher's exact test when appropriate. All analyses were two tailed, and p-values of 0.05 or less were considered to be statistically significant.

Results

A) Epidemical features

In our study, the oldest of the infected children was 108 months, while the youngest was 9 months, mean age was 39.5 months (39.5±25). Pre-school children (36-72 months) were 16(30.2%). Toddler period children (12-35 months) were 23(43.4%). More than 6 months and younger than 12 months were 7(13.2%). Ratio rate between boys and girls is 1.3:1. Most of the children came from city (Table 1). According to the last 9-year data (Table 2) it shows the outbreak of HadV this winter in Jilin province of china.

B) Clinical characteristics

Among the 53 children, 30 were in poor general condition at admission, 2 were drowsy, 30 were refused to eat or dehydrate, and 37 were dyspnea. Among which 28 were given oxygen by mask, 7 were given continuous positive airways pressure "CPAP", 2 were given mechanical ventilation. 53 had cough, 20 had wheezing, 3 had abdominal distension, and 8

had pleural effusion. The mean duration of fever time was 12.4 days (12.4 ± 6.1), and the mean maximum temperature during fever was 40.1°C (40.1 ± 0.6). (Table 3)

According to the diagnostic criteria of the British Thoracic Society, the American Pediatric Infectious Diseases Society (PIDS) and the Chinese Medical Association on severe pneumonia in children, 30 of the 53 cases were diagnosed as severe pneumonia. There were 3 cases of severe pneumonia complicated with toxic encephalopathy, 3 cases of electrolyte disturbance, 2 cases of thrush, and 2 cases of anemia.

C Etiological characteristics

Eleven of the 53 children (20.7%) were diagnosed with human adenovirus type 7 infection by testing the BALF with the NGS technology.

The incidence of co-infection was 75% and it was more likely to occur in older children ($p=0.018$) (Table 4) (we defined co-infection as : (a) Other pathogens detected by seven respiratory virus antigens; (2) Other pathogens detected by second-generation sequencing; (3) Serum mycoplasma pneumoniae (MP) antibody $\geq 1:160$, or double serum antibody was 4 times higher or lower; (4) Chlamydia pneumoniae (CP) antibody $>1 \text{ S/CO}$; (5) Clearly visible fungal infection of the mouth or vulva; (6) Others: no clear pathogenic evidence was found, but the procalcitonin (PCT) over 1.0 ng/ml would also consider the bacterial infection). Among all kinds of co-infection pathogens, MP was the most common in 18 cases, followed by CP and RSV in 5 cases, others are listed in Table 5.

D Cell-mediated immunity

We detected the number of immune cells (including the absolute cell counts of $\text{CD3}^+\text{T}/\text{CD4}^+\text{T}/\text{CD8}^+\text{T}/\text{CD19}^+\text{B}$) in 28 children by flow cytometry. The results showed that the absolute counts of $\text{CD3}^+\text{T}$ cells and $\text{CD19}^+\text{B}$ cells were less than the lower limit of the reference range in 50% of children, and the absolute counts of $\text{CD4}^+\text{T}$ cells were less than the lower limit of the reference range in 64.3% of children (Table 6).

E) Changes under electronic bronchoscope

Electronic bronchoscopy, as a diagnostic and therapeutic procedure, plays an important role in children's respiratory diseases. According to expert consensus on interventional diagnosis and treatment of respiratory endoscopy for refractory pneumonia in children in China, children who meet one of the following conditions will be recommended for this examination : A) Electronic bronchoscope is feasible for accurate pathogen diagnosis in the case of poor efficacy and unknown pathogen after routine treatment and detection, and suspected infection of special pathogens co-infection or drug-resistant bacteria. B) 133

Obvious symptoms and signs of airway obstruction (such as decreased or disappeared breath sounds, tubular breathing sounds, fixed wheeze repeatedly, hypoxia and increased carbon dioxide, which are difficult to solve with conventional treatment. C) Imaging suggested that unilateral emphysema, mediastinal emphysema, unilateral or bilateral pulmonary consolidation caused by atelectasis and airway obstruction, especially small airway lesions such as disappearance of air bronchogram and tree bud sign in consolidation, could be intervened. D) Ventilator treatment presented significantly increased peak pressure, decreased tidal volume, poor oxygenation and spasmodic sputum aspiration cannot be relieved. E) mycoplasma pneumoniae, adenovirus, influenza virus and other infections are easy to cause damage to the airway mucosa, and there are many secretions, forming mucous bolts to block the airway, which is likely to cause occlusive bronchitis in the future[23].

Finally, a total of 37 infected children were examined by bronchoscopy, and 17 of them had tiny sputum bolts in small distal airways (subsegments and branches) or in alveolar lavage fluid (Picture A and Picture B). While for children not infected with 149 HAdV, 86 cases (the total number was 835) were observed with tiny sputum bolts in bronchoscopy or alveolar lavage fluid at the same time. In conclusion, the specificity of diagnosing adenovirus infection with tiny sputum bolts in bronchoscopy or alveolar lavage fluid was 45.9%. The incidence of tiny sputum bolts between HAdV group and non-HAdV group had statistical importance($p=0.000$). Besides, changes may be more complex with co-infection, such as longitudinal folds of mucous membranes and/or changes in granule proliferation when combined with MP and CP (Picture C and D).

F) Treatment

In terms of drug therapy, the use of IVIG in severe group can reduce the fever days which had no statistically significant difference with the non-IVIG in mild group ($p=0.907$).

G) Imaging performance and follow-up

After admission, all the 53 cases received pulmonary CT examination, which had the following characteristics: A) Double lobes pneumonia were common, with a total of 40 cases (75.5%) : B) The lower lobe of the left lung was the most easily affected, with a total of 34 cases (64.2%); C) There were 31 cases (58.5%) of eccentric mass and ground glass changes. In addition, there were 8 cases with pleural effusion (all with a small amount of unilateral pleural effusion), among which 6 cases were left pleural effusion. We followed up the patients for 6 months, 12 by CT and 41 by telephone call. In the CT follow-up group, 8 had “Mosaic sign” on lung CT (Picture E and F), and 4 shows mild uneven ventilation. In telephone follow-up group 31 recovered well and had no symptoms, 10 had cough and tachypnea after moderate level of daily activities.

Discussion

According to our study, 86.7% of children younger than 6 years old are infected, which is similar to previous studies [13, 24-27], and mainly concentrated between 6 months and 36 months, which may be because children in this age group will contact more people and led to a higher risk of infection. Children less than 6 months, however, infection in our study did not find, according to previous studies, this may be because the age children with a mother who give the antibodies against adenovirus have immunity [7, 28-31]. At the same time, we found that adenovirus infections are more likely to occur in boys, men and women in our study sex ratio of 1.3:1, similar to the Gray GC data such as[22].

Based on our and previous studies, HAdV infection occurs all year round, but the incidence is higher in winter and spring[7, 30, 31], while in southern China, adenovirus infection is usually high in summer[32]. We have the following hypotheses for the small outbreak of adenovirus in this winter: A) The virus may prefer a warm climate. Compared with previous years, the average temperature in northeast China this winter was higher and the precipitation was less, which may be one of the reasons for the epidemic; B) There have been few reports of adenovirus infection in northeast China in recent years, and the reduced immunity of the population to adenovirus may be the second reason for this outbreak.

In this study, 11 cases of infected children were confirmed to be infected with HAdV-7 by NGS test. Therefore, we speculated that the HAdV-7 was the epidemic strain that caused the outbreak of infection this winter.

Our study found that the incidence of co-infection was high, but there was no statistical difference in clinical data between the co-infection group and the single infection group, which was similar to previous reports[32, 33]. As for the high incidence of co-infection we consider the following aspects: A) According to our study, the cell-mediated immune ability had suppressed, because of that it's easy to get other pathogen infection; B) Nowadays, the pathogen detection methods we use are more and more advanced (for example, NGS

mentioned earlier in this paper), making the detection rate of various pathogens significantly higher than before, thus increasing the co-infection rate; C) PCT and C-reactive protein are higher in the study, which often indicate the bacterial infection and led to the widespread use of antibiotics, also had similar situation in other studies [33-35], for the immune function suppressed by HAdV children the use of antibiotics will further increase the possibility of other pathogen infection. To sum up, when encountering children who are highly suspected to be infected with HAdV, we should be more cautious about the use of antibiotics, especially when and how to use.

Electronic bronchoscopy has been widely applied in children with lung disease[36, 37]. which plays an important role in the diagnosis and treatment of diseases. When it's difficult to confirm the etiology, lower airway samples can be obtained through this examination and use newly-developing method such as the NGS to clarify pathogens. What's more the combination can guide the next step of treatment. In addition, the characteristics of airway mucosa and secretions observed under bronchoscope, combined with epidemiology, clinical features and other auxiliary examinations, can give suggestive opinions to preliminarily determine the pathogen.

In terms of treatment, there is a lack of specific antiviral drugs for HAdV infection, we mainly use IVIG to give immune support and blocking antigen. In our study, this method could make no significant difference between the febrile time of children in the severe pneumonia group and non-severe pneumonia group. As an antiviral drug, cidofovir has been reported as a treatment for HAdV infection in the United Kingdom, the United States and South Korea[38-40], but it has not been reported in China.

In the CT follow-up group, 8 children had severe sequelae after 6 months, presented as the typical "Mosaic sign" on CT, and 4 cases presented mild uneven ventilation. In the telephone follow-up group, 31 recover well, according to their parents, these children had no symptoms. However, in the rest of the telephone follow-up group (10 children), these children had cough and/or tachypnea even after a moderate level of daily activities. A Malaysian study followed up 18 children with adenovirus pneumonia infection for 2 years,

and the results showed that 22% had pulmonary sequelae[41], which has been confirmed by earlier studies[42, 43]. However, the follow-up time of our study is still short, and further follow-up is needed to observe the outcome and recovery.

This study has the following limitations: A) The sample size included is not large enough, which may lead to the deviation of the analysis results. B) Most of the samples have not been sequenced, so our conclusion of this year's local epidemic strains may not be accurate enough. C) We didn't collect the cell-mediated immunity data when the infected children at the recovery stage, lacking effective comparison. D) Not all clinical data were collected in this study, so the results may not reflect the reality.

Conclusion

A) Compared with previous data in our hospital, in the winter this year, a little outbreak happened in Jilin province of China. B) We 243 infer that HadV-7 may be the prevalent strain. C) Before we get accurate etiology diagnosis, combining with the clinical symptoms, accessory results, the micro-sputum-bolt seen in the BALF when doing the electronic bronchoscope can give us some hints of HAdV infection.

Abbreviations

HAdV: Human Adenovirus; BALF: Bronchoalveolar lavage fluid; CT: Computed tomography; IVIG: Intravenous immunoglobulin; DIF: Direct immunofluorescence RSV: Respiratory syncytial virus; NGS: Next-generation sequence; CPAP: Continuous positive airways pressure; MP: Mycoplasma Pneumoniae; CP: Chlamydia pneumoniae; PCT: Procalcitonin.

Declarations

Ethics statement

The study protocol was approved by the Ethical Review Committee of the First Hospital of Jilin University. All the samples and information we collected were authorized by the children's parents.

Consent for publication

Written consent to publish this case report and any accompanying images has been obtained from the patient's parents.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Not applicable

Funding

Not applicable

Authors' contributions

QQ, FM, CL came up the initial idea and collected the clinical data. MP, YM analyzed and interpreted the patient data. All authors read and approved the final manuscript.

Acknowledgements

We thank the help Liying Wang and Ying Wang, staff of Pediatric research institute of the First Hospital of Jilin University, had offered during the data collection in our study.

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Tables

Table 1 Epidemic features

Group	number
Gender	
Male	30 56.6%
Female	23 43.3%
Ratio(male to female)	1.3:1
Age(months)	39.5±25
<6	0
6-12	7 13.2%
12-36	23 43.4%
36-72	16 30.2%
72-120	7 13.2%
>120	0
Place of residence	
City	47 88.7%
Rural area	6 11.3%

Table 3 Clinical characteristics

Group	number/mean±SD
Duration of fever(°C)	12.4±6.1
Highest temperature(°C)	40.1±0.6
Bad general status	30
Cough	53
Wheeze	20
Dyspnea	37
Mask oxygen inhalation	28
CPAP	7
Mechanical ventilation	2
Abdominal distension	3
Pleural effusion	8
Drowsiness	2
Apastia or dehydrate	30
Convulsion	3
Mild pneumonia	23
Severe pneumonia	30
Toxic encephalopathy	3
Electrolyte disturbance	3
Thrush	2

Table 4 Co-Infection situation

Group	number/mean±SD	p value
Co-Infection	40(75.5%)	
Age of single infection(month)	25.0±12.7	
Age of co-infection(month)	44.3±26.4	p=0.015

Table 6 Function of cell-mediated immune system

Group	number/mean±SD
CD3+ T cells(/ul)	1694.0±1070.5
CD4+ T cells(/ul)	870.8±642.6
CD8+ T cells(/ul)	939.1±1208.3
CD19+ B cells(/ul)	575.2±479.2

Reference range:CD3+ T cells(/ul):1500-3200

CD4+ T cells(/ul):1000-2100

CD8+ T cells(/ul):450-1100

CD19+ B cells(/ul):500-1200

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