Original Article

Epidemiology and transmission characteristics of human adenovirus type 7 caused acute respiratory disease outbreak in military trainees in East China

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Abstract: Background: Human adenovirus type 7 (HAdV7) is globally attracting great concern as its high morbidity and severity in respiratory diseases, especially in Asia. Objective: To investigate the clinical and epidemiologic characteristics of HAdV7 infection outbreak in East China. Methods: The clinical samples were collected from the patients of an ARD outbreak in East China for the detection of causative pathogens by multiplex PCR. The molecular type of human adenovirus isolates were identified by sequencing and homologous comparison based on their hexon genes. The spatiotemporal dynamics of global HAdV7 was investigated using the phylogenetic and phylogeographic analyses. Total 67 referenced HAdV7 hexon sequences (>800 bp) from GenBank were selected for constructing the maximum likelihood tree by MEGA 5.1.0, grouped according to the tree topology for the further migration analysis by PAUP* 4.0 and MigraPhyla 1.0 b to understand the transmission patterns of HAdV7 in global epidemics. Results: The results showed HAdV7 as the causative pathogen in this outbreak, and the outbreak strains had the hexon sequences highly identical with the isolates in Shaanxi (2012). The origin of HAdV7 was inferred as California, meanwhile a total of 21 migration routes were acquired. HAdV7 in this outbreak was statistically proven dispersed from Shaanxi province (2012). Conclusions: The analyses of epidemiology and transmission pattern of HAdV7 would not only enrich the molecular biological basic database but also provide theoretical basis for HAdV7 prevention and control strategy.

Keywords: Human adenovirus type 7, epidemiology, clinical characteristics, phylogeny, phylogeography

Introduction

Human adenovirus (HAdV) is a common virus found worldwide since it was first isolated from the tonsils and adenoids in children undergoing tonsillectomy and adenoidectomy in 1953 [1]. It is a non-enveloped icosahedral virus composed of double stranded linear DNA. Based on characteristics such as serology, DNA sequence homology, and phylogenomics, to date, more than 60 serotypes have been identified and classified into seven species (A-G, with B species further divided into B1 and B2 sub-species) [2].

Human adenovirus strains are widely distributed. HAdV infections are transmitted through respiratory route or the fecal-oral route, and
cause a broad spectrum of clinical diseases, including respiratory, gastrointestinal, conjunctival illness, etc [3, 4]. The children under the age of 5 years, close-quartered populations such as crowded communities, schools, military training camps, and immune-compromised individuals are generally the susceptible populations of the HAdV-infections according to the infectious route and pathogenicity [5, 6].

HAdV infections have been considered for decades as being one of the predominant causes (other two viral agents are respiratory syncytial virus, parainfluenza virus) of respiratory diseases among military trainees worldwide with infection reports in USA [7, 8], Asia [9] and Europe [10]. The HAdV serotypes most frequently associated with acute respiratory diseases (ARD) in both military and civilian communities have been reported as subspecies B1 HAdV3, HAdV7, HAdV21 and species E HAdV4 [7-9]. In the last 5 years, especially among the Asian area, a large scale population suffered from HAdV7 infections presented as ARD were reported continuously [11-13]. In mid-January 2014, another large scale of HAdV7 outbreak occurred in the military in east China. This apparent outbreak promoted us to use surveillance to describe the epidemiology, clinical features of HAdV7 infection. In the present study, we also investigated the transmission dynamics of HAdV7 from the origin to its dispersal in east China based on the phylogenetic and phylogeographic analyses [14, 15]. We aimed to understand the evolutionary process of HAdV7 in China, which will aid in establishing more effective control strategies.

Materials and methods

Samples collection and etiology determination

Totally 119 double throat swabs and blood samples were collected from the hospitalized military trainees who had the ARD symptoms such as fever (over 37.7°C), cough, cough with sputum and sore throat in Zhejiang and Shanghai, East China. All specimens were preserved at -80°C for subsequent nucleic acid extraction, viral culture and isolation. The study was approved by the Hospital’s Human Use Committee and Institutional Review Board.

All the blood samples were subjected to microbe culture, routine blood examination including blood cell count, blood platelet count, hemoglobin test, and C-reactive protein (CRP), blood biochemical tests, for example, albumin (ALB), total bilirubin (TBIL), glutamic-pyruvic transaminase (GPT), creatinine (Cr), and glucose (GLU). Acute IgM/IgG serology was evaluated by using enzyme-linked immunosorbent assay (ELISA) to detect the common respiratory pathogens including adenovirus.

PCR detection, meanwhile, was performed to confirm the causative pathogens. Viral nucleic acids were extracted from 200 ul of the throat swab specimens using the QiAmpMinElute Virus Spin Kit (QIAGEN, Shanghai, China) in accordance with the manufacturer’s instructions. For detection of Legionella pneumophila (L. pneumophila), Mycoplasma pneumoniae (M. pneumoniae) and Chlamydia pneumoniae (C. pneumoniae), previously published specific primers and probes targeted at specific regions of the mip gene, the P1 gene, and the 16S rRNA, respectively were used for real-time PCR assay [16-18]. Real-time PCR was performed on an ABI 7500 FAST Real-Time PCR System (Applied Biosystems, CA, USA). Amplification was according to the following parameters: 95°C for 10 min, followed by 50 cycles at 95°C for 15 s, 50-65°C for 1 min. Other 15 types of respiratory DNA/RNA virus were detected by using the Revert Aid First Strand cDNA synthesis kit (Fermentas, Ontario, Canada) and the Seeplex RV 15 ACE Detection Kit (Seegene, Seoul, Korea) in accordance with the manufacturer’s instruction.

Adenovirus culture, isolation and identification

From adenovirus-positive throat swab specimens identified by PCR analysis, 20 were randomly selected for incubating into HEp-2 cells and cultured in a maintenance medium (minimal essential medium containing 2% FCS, 100 U/mL penicillin G, 100 mg/mL streptomycin) at 37°C in a closed system in a 5% CO₂ incubator. Cultures exhibiting adenovirus-like CPE were passaged again to confirm the presence of the virus [13]. The genotype identification of HAdV was performed by sequencing and comparing the hexon gene sequence of the adenovirus positive isolate with that of other reference strains from NCBI GenBank database (http://www.ncbi.nlm.nih.gov/pubmed/). PCR amplification was optimized [19], and 3 pairs of specific primers were used for separate PCRs
Table 1. Primers used for amplification and sequencing of the complete hexon of HAdV7 isolates in this study

<table>
<thead>
<tr>
<th>Primer</th>
<th>Sequence (5’-3’)</th>
<th>Position*</th>
<th>Size (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADV-1F</td>
<td>GAGGAGAAAGGAAGGTCG</td>
<td>18373-18392</td>
<td>1272</td>
</tr>
<tr>
<td>ADV-1R</td>
<td>TATGCCATCCAGAGGAAAC</td>
<td>19626-19645</td>
<td></td>
</tr>
<tr>
<td>ADV-2F</td>
<td>CAGGAGAACTTTGAGGCTTA</td>
<td>19372-19393</td>
<td>946</td>
</tr>
<tr>
<td>ADV-2R</td>
<td>CAGAGGAGGTAGTCGTTGAATGA</td>
<td>20297-20318</td>
<td></td>
</tr>
<tr>
<td>ADV-3F</td>
<td>TTTCACATCAAGTGGCTCA</td>
<td>20044-20064</td>
<td>1331</td>
</tr>
<tr>
<td>ADV-3R</td>
<td>GGGAAACGCTTGTCAAAGGT</td>
<td>21356-21375</td>
<td></td>
</tr>
</tbody>
</table>

Notes: *Position in the complete genome of HAdV7 strain Gomen (AY594255).

whose products had overlapping sequences of 250-300 bp and were sequenced in both directions (Table 1). These sequence segments were assembled using the SeqMan in Lasergene 8 (DNASTAR, Madison, WI, USA). Multiple nucleotide sequence alignments were conducted by Clustal W in BioEdit 5.0.9 (Ibis Therapeutics, Carlsbad, CA, USA) [20]. 17 reference sequences representing seven species of HAdVs were retrieved from GenBank database and neighbor-joining phylogenetic tree with 1000 bootstrap pseudo-replicates was constructed based on the hexon gene sequences of the isolates from this outbreak by using MEGA 5 (CEMI, Tempe, AZ, USA) [21].

Migration analysis of human adenovirus type 7

The HAdV7 global transmission characteristics in the human populations were investigated by phylogenetic and phylogeographic analyses that were firstly used by Wallace et al. [22]. A total of 66 HAdV7 sequences were acquired for the construction of the HAdV7 data set according to 3 selection criteria: 1) the sequences searchable in the NCBI were published before January 2014, with the genome lengths ranging from 800-35000 bp; 2) the strains collected from sporadic HAdV7 infectious cases or without clear isolated information would be excluded; 3) the replicates (100% identity) at the same epidemic would be excluded. The HAdV3 isolate AB330084 from Genbank database was added into the data set of the HAdV7 strains (n=67) as an outgroup in the phylogeny. The maximum likelihood tree was constructed using a Kimura 2-parameter model by the bootstrap method with the value of 1000 replicates in MEGA 5 (CEMI, Tempe, AZ, USA). Then 67 referenced sequences used in the migration analysis with MigraPhyla 1.0 b (http://pd.bio.uci.edu/ee/WallaceR/Migraphyla.html) [14] were grouped into 32 discrete modules, each of which was combined with the year of isolation and the isolated locality according to the tree topology [22]. The modules of the sequences in the tree were assigned to the tips as a single character with 31 states. And the modules of ancestral nodes were assigned by the method of maximum parsimony in PAUP* 4.0 (Sinauer Associates, Sunderland, MA, USA) when moving recursively up the tree to support the fewest possible migration events between modules consistent with the phylogenetic tree. Under the MigraPhyla protocol, a Monte Carlo test of 10000 trials was performed to calculate the $P$ values that represented the probable frequencies of migration events between each pair of modules in the original migration tree more than that of migration events between each pair of modules randomly distributed across the tree tips. Furthermore, to test the significance of $P$ values ($P<0.05$) across all localities, a corresponding sparse false discovery rate (sFDR) correction was calculated as the necessary for $\alpha$, the normal type 1 error rate in the multiple tests across module pairs.

Inpatient analysis

Complete clinical, radiographic, and laboratory examinations were performed in all the hospitalized trainees with permission. Relevant data were recorded, surveillance of radiographic examinations including routine thoracic computed tomography (CT) scans, ultrasound and electrocardiographic examination on the patients were kept during the treatment. These analyses were aim for determining whether HAdV infection was associated with specific presenting or outcome variables.

Statistical analysis

Data were analyzed by SPSS version 11.02 (SPSS, IL, USA). Categorical variables were used for description of the clinical data, and continuous variables were signed as ($\bar{x} \pm SD$). Monte Carlo test of 10000 trials were applied in Migration analysis to calculate the value of $P$. A value of $P<0.05$ was considered statistically significant.
Epidemiology and clinical features of ARD infection

In mid-January 2014, an ARD outbreak occurred in the military training bases where a total of 1200 soldiers were taking the training in Zhejiang and Shanghai, China. Centralized teaching courses and training activities were carried out for recruit trainees. The index cases were two recruits aged both 20 years who lived in the same dormitory presented with fever (oral temperature of 38.1°C, 38.5°C, respectively), and a series of ARD symptoms, including cough, sputum, sore throat, and headache. The disease spread rapidly and peaked 4 days after the index cases. Medical staffs from three military hospitals were sent to aid the base medics in treating the sick trainees. During this outbreak, 342 trainees aged 17-23 years developed disease symptoms. Infectious patients who had febrile respiratory symptoms with severe moist rales heard or shadows in the lung by fluoroscopy were suggested to be hospitalized. Remaining mild cases were reviewed by physicians, quarantined and treated in the training base. In this study, 119 ill trainees were hospitalized and their clinical features were summarized in Table 2. Among these hospitalized trainees, the most common symptom was fever (85, 71.4%). Neither gastrointestinal symptoms nor conjunctivitis was observed. Skin rash (1, 0.9%) and anorexia (3, 2.7%) were less common. In addition, cervical lymphadenopathy was detected in 10 (8.4%) patients.

Clinical laboratory parameters and radiographic findings

The results of blood culture showed all blood samples were negative for microbe. The routine blood examination exhibited abnormal white blood cell (WBC) levels including Leukocytosis (>10.0×10⁹/L, 12.61%) and leukopenia (<4.0×10⁹/L, 31.93%), and elevated C-reactive protein (CRP, >5.0 mg/L). No obviously abnormal biochemical indexes were observed. Six kinds of pathogen-specific IgM antibodies were detected. All samples were positive for HAdV IgM, 4 were simultaneously positive for M. pneumoniae IgM, and one each positive for IgM specific to L. pneumophila, C. pneumoniae, influenza A virus and human parainfluenza virus, respectively. Further chest radiography that performed in all inpatients was reviewed. 53 chest abnormal cases were observed by chest CT scan at admission. Besides, another 5 patients hospitalized for 2 days with worsen conditions were found chest abnormal. In summary, 48.7% (58/119) patients signed as pneumonia. By reading the film results of chest CT scan, high density mottling or patchy shadows were predominantly existed rather than homogenous lobar or segmental shadows, which were mainly distributed as a unilateral lung form, especially in the left lung (26, 21.8%) (Figure 1A and Table 2). Besides, similar patchy shadows were observed in the right lung (18, 15.1%) (Figure 1C and Table 2), and in bilateral lungs (12, 10.1%) (Figure 1E and Table 2).

PCR determination of the outbreak

By detecting the causative pathogens using extracted nucleic acid from 119 throat swab...
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From 20 randomly selected adenovirus-positive throat swab specimens identified by PCR analysis, 18 isolates were observed to produce visible adenovirus-like CPE upon culturing in A549 cells. Comparative analysis and online Nucleotide BLAST analysis of the entire hexon sequences showed that all these 18 outbreak isolates shared 100% similarities with each other and were identified as the same genotype HAdV7, of which 3 representative isolates from different time points (16 January, 20 January and 27 January) were archived as HZU2014-07, HZU2014-23 and HZU2014-81, and deposited in GenBank with the corresponding accession number KP337345, KP337346, and KP337347. Further, phylogenetic analysis results showed that the isolates from this study belonged to HAdV7 and had high identity with the hexon gene of HAdV SXWN1203 strain KC689913 [13], HAdV CHN/DG01/2011/7 [P7H7F7] strain KC440171 [Figure 2] [23].

Molecular analysis of human adenovirus

From 20 randomly selected adenovirus-positive throat swab specimens identified by PCR analysis, 18 isolates were observed to produce visible adenovirus-like CPE upon culturing in A549 cells. Comparative analysis and online Nucleotide BLAST analysis of the entire hexon sequences showed that all these 18 outbreak isolates shared 100% similarities with each other and were identified as the same genotype HAdV7, of which 3 representative isolates from different time points (16 January, 20 January and 27 January) were archived as HZU2014-07, HZU2014-23 and HZU2014-81, and deposited in GenBank with the corresponding accession number KP337345, KP337346, and KP337347. Further, phylogenetic analysis results showed that the isolates from this study belonged to HAdV7 and had high identity with the hexon gene of HAdV SXWN1203 strain KC689913 [13], HAdV CHN/DG01/2011/7 [P7H7F7] strain KC440171 [Figure 2] [23].

Clinical treatment and prognosis

According to the clinical symptoms and signs, HAdV7 was determined as the causative pathogen for this outbreak in the military training bases combining with the laboratory results. Following the diagnosis and treatment guideline for adenovirus infection issued by Chinese Military Commission for Infectious Diseases [24], we used the treatments such as, methylprednisolone sodium succinate (methylprednisolone) for anti-inflammatory, ribavirin for antiviral, levofloxacin lactate (laiixin) for preventing infection, tanreqing (a Chinese patent medicine) treatment, vitamin C for heat clearing and detoxifying, rebamipide tablets for protecting gastric mucosa, omeprazole enteric coated capsules for inhibition of gastric acid. All HAdV7 infectious patients received the same antibiotic treatment exclude the ones who were co-infected with M. pneumonia or C. pneumonia or L. pneumophila were added the extra azithromycin to the antibiotic treatment.

Migration analysis of human adenovirus type 7

As described, MigraPhyla was used for tracking the migration of HAdV7 during its evolutionary history [14, 22]. Total 67 sequences (excluding the replicates in the same epidemic and individual infectious cases) in 31 modules across 19 localities worldwide from its first discovery
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Figure 2. Neighbor joining phylogeny of hexon sequences for HAdV7 isolates described in this study and other reference hexon sequences representing seven species of HAdV from GenBank.

Discussion

In the present study, we reported a large-scale outbreak of HAdV7 infections associated with acute respiratory disease in a military training base in Zhejiang Province and Shanghai, East China, in mid-January, 2014. Compared with the clinical symptoms that published previously, symptoms in this epidemic showed no apparent difference, such as fever, cough, expectoration, and pneumonia [5, 25, 26]. Positive HAdV-IgM in serum samples from patients were determined, however could not be used as an early diagnosis for infection. As described by Julkunen et al., IgM responses were faint and inconsistent comparing with IgA and IgG responses [27]. Therefore, the IgM antibodies test by ELISA was not appropriate for the early diagnosis of HAdV infection. We took the multiplex PCR approach by using the Dual priming oligonucleotide system technology for detecting the adenovirus [28], and identified the molecular type of HAdV by using direct sequenc-
of the hexon gene where the hypervariable regions (HVRs) were existed. Up to now, this hexon gene sequencing and homologous analysis is the most traditional but highest accurate method for identification of HAdV [29]. However, compared to other type-specific PCR or nested PCR methods, it also costs much and is time-consuming on the cases of numerous clinical specimens. Therefore, the need to establish and improve the efficient epidemiological and common etiological detection for HAdV infection is emphasized.

Among HAdV serotypes, HAdV3, HAdV7, HAdV21 and HAdV4 have been reported to cause outbreaks of respiratory infection in close-quartered populations including civilian communities, hospitals, schools, and military who mostly recovered with no residual sequelae [8, 30, 31]. HAdV7 is of particular concern as it is often with more severe or higher levels of morbidity in the related respiratory diseases than other HAdV serotypes [23]. In recent 5 years, relevant reports of the outbreaks of HAdV7 associated ARD that affect large population trend to be increased [11-13]. In mainland China, epidemic outbreaks of HAdV7 that affected numerous of military recruits, populations in schools or hospitals consecutively occurred in Chongqing (2010) [23], Guangzhou

Figure 3. Maximum likelihood phylogeny of hexon sequences of HAdV7 viruses from this study in Hangzhou, China and other global locations. 66 HAdV7 hexon sequences across the world in different years from Genbank were analyzed.
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(2011) [23], Shijiazhuang (2011) [32], Beijing (2012-2013) [33], Shaanxi (2012) [13], Hangzhou (2014) (In this study). In this outbreak, the genotype of HAdV isolates was identified as HAdV7 through phylogenetic analysis, and each hexon gene of the isolates were identical, these isolates also had high identity (100%) with the HAdV SXWN1203 strain KC689913.1 [13] and the HAdV CHN/DG01/2011/7 [P7H7F7] strain KC440171 (Figure 2) [23]. Homologous analysis also performed on the sequence data set of global HAdV7 hexon genes, these results indicated not only the very low mutation frequency of HAdV7 isolates during the epidemic, but also the relative low mutation rate in the evolutionary history.

It has been known that viral infection has close relationships with the body immune competence [34]. Once the virus invades the body, human adaptive immunity is activated, mainly through 2 pathways including the re-infection and vaccination. During the re-infection of human adenovirus, it has been reported that most serotypes of the human adenovirus cause multi-system infections including respiratory, gastrointestinal, and central nervous system infections that are commonly mild or recessive infections. These are consistent with the neutralizing antibody responses to HAdV. Neutralizing antibodies that are produced after viral infection indicate the nature of persistent protective immunity in humans to HAdV infection [34]. As described, HAdV7 vaccines played a significant role in defense and decrease of adenovirus infection after the first application in the USA military recruits in 1971 and the reuse of HAdV7 vaccines in late 2011 [35, 36]. According to the Naval Health Research Center (NHRC) ongoing adenovirus surveillance, the resumption of the vaccines in recruits made adenovirus rate plummeting from 5.8 to 0.02 cases per 1000 person-weeks in 2012-2013 [36]. This finding confirmed the effectiveness of the vaccines in prevention of HAdV7 infection.

By now, there have been no relevant reports or experimental data from the perspective of either the virus’s victims or the virus alone inferring the transmission patterns of HAdV7 in the epidemic all over the world. And this is the first time temporal and spatial transmission dynamics of HAdV7 across the world has been investigated by phylogeographic analysis. MigraPhyla results showed that among 56 observed HAdV7 migration routes, 22 migration ro-

Figure 4. Global migration maps of HAdV7 hexon sequences that related to this outbreak. The node denotes the locality, the red solid arrow lines indicate the statistically significant routes between two nodes (P<0.05) under 10000 Monte Carlo tests and a sparse false discovery rate (sFDR) correction.
HAdV7 hexon gene sequences or unclear HAdV7 isolates in some epide-
mics were exclude to the migration analysis of HAdV7 globally, the possibility of other trans-
mission routes are needed for further research and confirmation.

Conclusions

Our study reported a large scale HAdV7 out-
break in Chinese military and reviewed the high
frequency of HAdV7 infections in Asia (espe-
cially in China) in the last 5years. Phylogenetic
and phylogeographic analyses of HAdV7 glo-
ally play an important role in learning the
human adenovirus world and create a founda-
tion towards exploitation of the more effective
HAdV7 molecular diagnosis reagents and the
relevant vaccines, also offered valuable ac-
cordance for HAdV7 prevention and control stra-
gy. By recognizing the benefit for the applica-
tion of the effective vaccines in preventing the
transmission of HAdV in USA, the development
of AdVvaccines and vaccination application in
the most vulnerable groups including students,
recruits and community population in Asia
(especially in China) should be emphasized.

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Disclosure of conflict of interest

None.

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