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Clinical analysis of adenovirus pneumonia with pulmonary consolidation and atelectasis in children

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Abstract

Objective: To assess the clinical characteristics of 168 children with adenovirus pneumonia complicated by pulmonary consolidation and atelectasis.

Methods: We retrospectively studied patients with adenovirus pneumonia complicated by pulmonary consolidation and atelectasis admitted to Xiamen Children's Hospital from March 2019 to August 2019. In total, 168 patients were recruited and divided into a severe group and non-severe group according to disease severity. Clinical results were assessed.

Results: All children had fever and cough, 29 had wheezing, and 82 had dyspnea. Pleural effusion was found in 53 patients. Mixed infections were present in 95 patients. A total of 105 patients received hormone therapy, 72 received intravenous gamma globulin, and 103 underwent bronchoscopy, among whom 6 were found to have bronchial casts. Of the 168 children, 166 were cured and two died. The patients were divided by disease severity, with 82 in the severe group and 86 in the non-severe group. The two groups showed significant differences in the fever course, pleural effusion, mixed infections, hemoglobin concentration, procalcitonin concentration, and lactate dehydrogenase concentration.

Conclusion: A long fever course, mixed infection, pleural effusion, decreased hemoglobin concentration, and increased procalcitonin and lactate dehydrogenase concentrations may be associated with more severe adenovirus pneumonia.

Keywords

Children, adenovirus pneumonia, pulmonary consolidation, atelectasis, severe case, fever

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Introduction

Pneumonia is a common disease that endangers children's health and is a significant cause of death in children under 5 years of age. Adenovirus (ADV) is an important pathogenic cause of pneumonia in children. ADV is prevalent worldwide; 3.5% to 11.0% of pediatric cases of pneumonia are caused by human ADV.[1–3] ADV7 is especially virulent and often leads to severe ADV pneumonia, which is a serious threat to children's health. Pulmonary consolidation and atelectasis are characterized by a reduction in the volume/air content of one or more lung segments/lobes. Pulmonary consolidation and atelectasis are not independent diseases but often occur as a complication of various chest diseases. ADV infection can easily cause pulmonary consolidation and atelectasis and thus requires a high level of vigilance by pediatricians. This disease is refractory, and some children may have residual airway occlusion even after they have been cured, resulting in chronic airway disease. To explore the clinical characteristics and treatment experience of ADV pneumonia complicated by pulmonary consolidation and atelectasis in children, we retrospectively analyzed the medical histories, physical signs, auxiliary examination findings, and diagnosis and treatment processes of children hospitalized in Xiamen Children's Hospital from March 2019 to August 2019. Our hope is to improve doctors' understanding of this disease, thus allowing for refinements in interventions and treatments, a reduction in the incidence of critical cases in children, and an improvement in children's prognosis.

Patients and methods

Patients

This retrospective study involved consecutively selected patients with ADV pneumonia complicated by pulmonary consolidation and atelectasis who were admitted to Xiamen Children's Hospital from March 2019 to August 2019. According to their disease severity, the patients were divided into a severe group and non-severe group. Patients who were discharged spontaneously before the end of treatment were excluded from the study.

This study was approved by the institutional review board and the Ethics Committee of Xiamen Children's Hospital, Xiamen, Fujian Province, China ([2020] No. 038). Written informed consent for treatment was obtained from all patients. The need for informed consent for research was waived by the committee because of the retrospective design of the study, and all data were de-identified.

Diagnostic basis

Diagnostic criteria for ADV pneumonia. The diagnostic criteria for pneumonia in the present study were based on the *Diagnostic and Treatment Standards for Adenovirus Pneumonia in Children (2019 Edition)*[4] issued by China's National Health Commission and National Administration of Traditional Chinese Medicine. The diagnostic criterion for ADV was a nasopharyngeal swab or alveolar lavage fluid test that was positive for ADV antigen using immunofluorescence assay or a nucleic acid test.

Diagnostic criteria for pulmonary consolidation[4]. Pulmonary consolidation was diagnosed when both of the following criteria were met. (1) The patient's main clinical manifestation was dyspnea. (2) Pulmonary high-resolution computed tomography (CT) showed clustered pulmonary consolidation shadows in both lungs, most of which had a centripetal distribution. The lung lobes with consolidation had a relatively high density, and air bronchograms could usually be observed.

High-resolution CT diagnostic criteria for atelectasis[5]. Atelectasis was diagnosed with either direct or indirect findings were present on high-resolution CT. (1) Direct signs of atelectasis: increased density of involved lung segments or lobes, clear and sharp edges, displacement of interlobar fissures, and significant enhancement on enhanced scanning. (2) Indirect signs of atelectasis: hilar displacement, mediastinal shift, diaphragmatic elevation, blood vessel convergence, excessive inflation of other normal lung tissues, and narrowing of the intercostal space.

Diagnostic criteria for severe pneumonia[6]. Severe pneumonia was diagnosed when any of the following criteria were met. (1) Poor general condition. (2) Conscious disturbance. (3) Cyanosis or tachypnea [age of <2 months: respiratory rate (RR) ≥ 60 breaths/minute; age of 2 months to 1 year: RR ≥ 50 breaths/minute; age of 1–5 years: RR ≥ 40 breaths/minute; and age of >5 years: RR ≥ 30 breaths/minute), intermittent apnea, or oxygen saturation of $<92\%$. (4) Ultrahyperpyrexia or persistent hyperpyrexia for more than 5 days. (5) Dehydration or refusal of food. (6) Pulmonary infiltration of at least two-thirds of the lung, pneumothorax, lung necrosis, or lung abscess on one side as revealed by chest X-ray or CT. (7) Extrapulmonary complications.

Etiological detection. Etiological examinations included blood culture, sputum culture, and respiratory pathogenic detection (including ADV, respiratory syncytial virus, influenza virus A and B, and parainfluenza virus 1 to 3).

Research methods

All children with ADV pneumonia complicated by pulmonary consolidation and atelectasis were divided into a severe group and non-severe group according to their disease severity. The patients' clinical manifestations, laboratory examination findings, imaging data, treatment plans, efficacy, outcomes, and other data were summarized and analyzed.

Statistical methods

IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Measurement data that did not conform to a normal distribution are expressed as median, and the non-parametric Kruskal–Wallis test was used for comparisons between the severe group and non-severe group. Enumeration data are expressed as frequency and percentage, and the χ^2 test was used to examine differences between patients with severe and non-severe disease when adopting different grouping methods. A P value of <0.05 was considered statistically significant.

Results

Demographic characteristics

From March 2019 to August 2019, 168 children were definitively diagnosed with ADV pneumonia complicated by pulmonary consolidation and atelectasis in our hospital. The patients' age at disease onset ranged from 1 month to 5 years 6 months, and the median age was 2 years 7 months (range, 5 months to 9 years). Sixty-eight (40.48%) children were aged ≤ 2 years and 100 (59.52%) were aged >2 years. The children comprised 90 (53.57%) boys and 78 (46.43%) girls, with a male:female ratio of 1.15:1.00.

Clinical manifestations

All 168 children had a fever and cough, 29 had wheezing, and 82 had dyspnea. The fever course lasted <10 days in 99 (58.93%) children and ≥ 10 days in 69 (41.07%) children. The clinical condition of 53 (31.55%) children was complicated by pleural effusion.

Imaging examinations

Among the 168 children, 84 (50.0%) had pulmonary consolidation and atelectasis in a single lobe, including 11 (6.55%) in the right upper lobe, 6 (3.57%) in the right middle lobe, 24 (14.29%) in the right lower lobe, 11 (6.55%) in the left upper lobe, and 32 (19.05%) in the left lower lobe. Eighty-four (50.0%) children had multiple consolidation and atelectasis in two or more lung lobes. Pleural effusion was found in 53 (31.55%) children.

Mixed infections

Among the 168 children, 95 (56.55%) had mixed infections, including 21 (12.5%) cases of mixed *Streptococcus pneumoniae* infection, 27 (16.07%) cases of mixed *Haemophilus influenzae* infection, 10 (5.95%) cases of mixed *Staphylococcus aureus* infection, 3 (1.79%) cases of mixed *Moraxella catarrhalis* infection, 28 (16.67%) cases of mixed *Mycoplasma pneumoniae* infection, 3 (1.79%) cases of mixed respiratory syncytial virus infection, and 3 (1.79%) cases of mixed fungal infection.

Treatments

After confirmation of the diagnosis, all children were treated with antipyretics, rehydration therapy, aerosol inhalation, sputum suction, and other therapies. Patients whose condition was complicated by bacterial or *Mycoplasma pneumoniae* infection were administered corresponding anti-infective treatments. Among the 168 children, 105 (62.5%) received hormone therapy, 72 (42.9%) received intravenous gamma globulin, and 103 (61.3%) underwent bronchoscopy and alveolar lavage, among whom 6 were found to have bronchial casts. During the treatment, mechanical ventilation was provided for 29 patients, and their length of hospital stay ranged from 7 to 31 days. Among the 168 children, 166 (98.81%) were cured and discharged from the hospital and 2 died (respiratory failure in 1 patient and toxic encephalopathy in 1 patient).

Comparison between children in severe and non-severe groups

The 168 children were divided into two groups according to their disease severity: the severe group [82 (48.81%) patients] and the non-severe group [86 (51.19%) patients], and the clinical data of the two groups were compared. As shown in Table 1, there was no significant difference in sex, age, or lung lobe involvement of pulmonary consolidation and atelectasis between the severe group and non-severe group. However, there were significant differences in the fever course, pleural effusion, and mixed infections between the two groups; i.e., patients with a longer fever course, mixed infections, and pleural effusion were more likely to progress to severe disease ($P < 0.001$, 0.001, and $P = 0.001$, respectively).

The laboratory indicators are compared between the non-severe and severe groups in Table 2. Among the laboratory examination indicators, no significant difference was found in the white blood cell count, platelet count, C-reactive protein concentration, or erythrocyte sedimentation rate between the severe group and non-severe group. However, the hemoglobin (HGB), procalcitonin (PCT), and lactate dehydrogenase (LDH) concentrations showed significant differences; specifically, a lower HGB concentration and higher PCT and LDH concentrations were associated with a greater possibility of progression to severe disease ($P = 0.003$, and $P < 0.001$ and 0.001, respectively).

Discussion

ADV pneumonia is a common childhood viral pneumonia with a specific seasonal epidemic trend. In China, it occurs frequently in winter and spring, which are reportedly the seasons in which the

Table 1. Comparison of clinical data of 168 children with severe versus non-severe adenovirus pneumonia complicated by pulmonary consolidation and atelectasis.

Parameter	Classification	Non-severe group	Severe group	χ^2	P
Sex	Male	45 (52.3)	45 (54.9)	0.11	0.74
	Female	41 (47.7)	37 (45.1)		
Age	≤2 years	30 (34.9)	38 (46.3)	2.287	0.13
	>2 years	56 (65.1)	44 (53.7)		
Fever course	≥10 days	19 (22.1)	50 (61.0)	26.221	<0.001
	<10 days	67 (77.9)	32 (39.0)		
Lung lobe involvement	Single lobe	44 (51.2)	40 (48.8)	0.095	0.758
	Multiple lobes	42 (48.8)	42 (51.2)		
Pleural effusion	Yes	11 (12.8)	42 (79.3)	28.705	< 0.001
	No	75 (87.2)	40 (20.7)		
Mixed infections	Present	38 (44.2)	57 (69.5)	11.452	0.001
	Absent	48 (55.8)	25 (30.5)		

Data are presented as n (%).

Table 2. Comparison of laboratory examination indicators of 168 children with severe versus non-severe adenovirus pneumonia complicated by pulmonary consolidation and atelectasis.

Parameter	Severe group (n = 82)	Non-severe group (n = 86)	Z	P
WBC, $\times 10^9$/L	8.370 (2.1–19.38)	9.26 (2.23–25.30)	3.549	0.559
HGB, g/L	102.0 (87–168)	117 (88–245)	8.813	0.003
PLT, $\times 10^9$/L	262.0 (78–727)	270 (112–670)	3.858	0.591
CRP, mg/L	8.315 (0–143.3)	7.775 (0.5–106)	3.668	0.651
ESR, mm/h	32.0 (5–94)	33.5 (5–72)	1.507	0.220
PCT, ng/dL	0.6 (0.04–15.44)	0.405 (0.04–11.02)	17.339	<0.001
LDH, U/L	409.15 (198–3000)	343 (204–2713)	21.441	<0.001

Data are presented as median (range).
WBC, white blood cell count; HGB, hemoglobin; PLT, platelet count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; LDH, lactate dehydrogenase.

incidence of infection is highest in the southern regions of China such as Suzhou and Guangzhou.[7,8] The seasonality of ADV pneumonia is similar in other parts of the world.[9] The epidemiological characteristics of ADV pneumonia complicated by pulmonary consolidation and atelectasis are similar to those of uncomplicated ADV pneumonia. All patients in the present study were children under 6 years of age, and the incidence tended to be higher in male than female patients. These characteristics are highly consistent with those of uncomplicated ADV pneumonia. According to our analysis, the reason for the higher susceptibility in young children and infants is related to their immature immune function, low anti-infection ability, and insufficient ability of the body to inhibit ADV replication.

The clinical symptoms of ADV pneumonia complicated by pulmonary consolidation and atelectasis vary in severity. Most affected patients show an acute onset with a recurrent high fever, cough, and expectoration to different degrees. Disease progression may lead to wheezing and even dyspnea. ADV

infection can cause damage to the internal membrane of bronchi. Bronchoscopy can reveal congestion and edema of the bronchial mucosa. Viscous secretions can be observed in the bronchial lumens, and some secretions form jelly-like sputum plugs, resulting in stenosis of the lumens. A bronchoscopic mucosal biopsy can reveal destruction of the ciliary structure and an unclear display of the $9+2$ arrangement of microtubules, suggesting local ciliary damage in the bronchi as well as dysfunctions in ciliary swinging and sputum excretion. Moreover, younger children have low coughing strength, resulting in sputum blockage and absorption of gas in the bronchi and alveoli below the blocked segment; this may progress to atelectasis.

As reported in the literature,[10] the lesions in patients with ADV pneumonia complicated by pulmonary consolidation and atelectasis are mainly seen in the lower left lobe on CT images and often involve more than two lobes. In the acute phase of pulmonary consolidation, the lesions are mostly clustered parenchymal shadows distributed centripetally in both lungs, with high consolidation density; air bronchograms can be observed in most consolidation shadows, and the patient's condition might be complicated by atelectasis, pneumothorax, mediastinal emphysema, and subcutaneous emphysema.[11] In the present study, 84 (50.0%) patients had lesion involvement in the bilateral lung lobes. Among the patients with single-lobe involvement, 32 (19.05%) had lesion involvement in the left lower lobe, ranking first in single-lobe lesions; this is similar to the findings reported in the literature. The formation and centripetal distribution trend of such clustered parenchymal lesions is related to the spread of human ADV infection along the airway through small and medium bronchi with involvement of the lung parenchyma and alveoli; this causes exudation of inflammatory substances and thus results in pulmonary consolidation and atelectasis.[12] In the present study, there were significantly more patients with pleural effusion in the severe group than non-severe group.

Patients with ADV pneumonia complicated by pulmonary consolidation and atelectasis have serious disease conditions as well as decreased immunity and resistance, and they can easily develop complicated infections. In particular, patients with respiratory failure require mechanical ventilation; thus, the incidence rate of secondary infection is even higher. The rate of mixed infections in the present study was as high as 56.55%. Lynch and Kajon[13] illustrated that during human ADV infection, nonspecific changes in the airway and a specific virus-mediated reaction between the bacteria and host are the main factors leading to mixed infections. The present study demonstrated that patients with clinical fever courses of $\geq$10 days, mixed infections, and pleural effusion were more likely to develop severe pneumonia. This is related not only to the pathogenicity of the virus but also to the immune response ability of the body. The activation of the immune system and the production of cytokines or inflammatory mediators play an essential role in the activation of inflammatory reactions and the mechanism of tissue damage.[14]

At present, there is no specific antiviral drug with which to treat ADV infection; therefore, symptomatic support is particularly important in patients with ADV infections. Patients should receive active antipyretic, expectorant, rehydration, and other treatments, and their clinical condition should be closely observed. The possibility of severe illness should be considered in patients with a persistent high fever, shortness of breath, or difficulty breathing. Gamma globulin or glucocorticoid therapy can regulate the body's immunity, neutralize antibodies, and accelerate the removal of ADV from the respiratory tract to a certain extent. In the present study, these treatments were applied to varying

degrees and achieved reliable efficacy. Of the 168 children, 103 (61.3%) received bronchoscopic lavage, which effectively improved the clinical symptoms and shortened the disease course in children with pulmonary consolidation and atelectasis. ADV pneumonia leads to necrosis and shedding of the bronchial mucosa, and necrotic matter blocks the lumens and aggravates ventilatory dysfunction. Bronchoscopic alveolar lavage can remove pathogens that have adhered to the airway surface by inflammatory media, effectively reduce direct and indirect pathogen-induced damage to the bronchial mucosa, and improve lung expansion. Six children in the present study developed bronchial casts. Bronchial casts are a serious complication of ADV pneumonia with pulmonary consolidation and atelectasis. If they are not identified and treated in time, they may be life-threatening. Bronchoscopic removal of the casts blocking the airway is the most direct and effective method for diagnosis and treatment.[15]

Comparison between the non-severe and severe groups in this study also showed that among the laboratory examination indicators, the HGB, PCT, and LDH concentrations were significantly different between the two groups; specifically, a lower HGB concentration and higher PCT and LDH concentrations were associated with a greater possibility of progression to severe disease. In children, anemia causes various organs and tissues to be in a state of anoxia and their function to decline. An increase in the PCT concentration suggests strong immune stimulation after ADV infection on the one hand and mixed bacterial infections on the other.[16] An elevated LDH concentration indicates cell lysis or cell membrane destruction of important organs (including the lungs).[17] The possibility of severe ADV infection should be considered in these situations.

This study had a certain degree of selection bias, including a small total number of patients, all of whom were diagnosed during the ADV outbreak period (March–June); additionally, the number of patients in the severe group was higher than that in the general population. Therefore, we need to further expand the sample size and eliminate bias in future studies.

In summary, ADV pneumonia complicated by pulmonary consolidation and atelectasis mainly manifests as a recurrent high fever, cough, shortness of breath, and even respiratory failure. Patients with long fever courses, mixed infections, pleural effusion, a decreased HGB concentration, and increased PCT and LDH concentration are more likely to progress to severe pneumonia. At present, there is no specific antiviral drug for ADV. Active symptomatic and supportive treatment, timely gamma globulin or glucocorticoid therapy, and fiberoptic bronchoscopy may be effective in improving clinical symptoms.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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