

The Effect of Therapeutic Bronchoalveolar Lavage in Combination with Glucocorticoids on Children with Acute Exogenous Lipoid Pneumonia

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Abstract

Background: Exogenous lipoid pneumonia(ELP) is a rare disease caused by the inhalation of oily materials in the alveoli with the pathological characterization by the presence of laden-lipid macrophages in the respiratory specimens. At present, the treatment norm for ELP has not well defined, and so the aim of this study is to evaluate the effect of bronchoalveolar lavage in combination with glucocorticoids on children with ELP. **Methods and Materials:** We retrospectively reviewed 17 children with a confirmed history of exogenous oily materials aspiration, admitted to the First Affiliated Hospital of Guangzhou Medical University from June 2012 to December 2021. Clinical features, blood investigations, tomographic evaluations, therapeutic bronchoalveolar lavage and glucocorticoids use were carried out at the beginning of therapy and throughout a follow-up period. **Results:** The included children are the median age of 2 years. Fever, dypnea and tachypnea were the most common symptoms. The most common radiological features were airspace consolidations(15, 93.75%). Chest CT scans showed areas of consolidation with air bronchogram(15, 93.75%), Poorly defined centrilobular nodules(13, 81.25%), areas of ground-glass attenuation(11, 68.75%), and ‘crazy-paving’ pattern(6, 37.5%) in the both lower, right middle lung lobes. Neutrophil percentage of peripheral blood and bronchoalveolar lavage fluid exhibited a significantly higher than the normal range. After treatment with multiple bronchoalveolar lavages and local administration of budesonide during the hospital stay, taken by oral prednisolone(1~2mg/kg) after discharge,all of children became asymptomatic and presented normal radiological imagings in the follow-up period. **Conclusion:**The most frequently findings in the CT scan of ELP were consolidations and ground-glass attenuation in the both lower and right middle lung lobes.Multiple bronchoalveolar lavages in combination with oral prednisolone for children who had a confirmed history of exogenous oily substances ingestion was an efficient and safe for the clearance of oily materials from the lung and the prevention of fibrosis. This strategy contributed to reducing the damage of ELP in children patients.

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Key Words: Bronchoalveolar Lavage; Exogenous Lipoid Pneumonia; Glucocorticoids Therapy; Children

1 Introduction

Lipoid pneumonia(LP) is a rare disease caused by inhalation or aspiration of oily substances and has been reported with an incidence of only 1%~2.5% in autopsy series.¹Based on the source of the lipid, LP is categorized as follows: Exogenous lipoid pneumonia(ELP), due to an episode of aspiration of a large quantity of a oil-based product; endogenous LP, related to uncommon medical conditions.^{2,3} Historically, Laughlen reported the first cases of exogenous lipoid pneumonia in one adult and in four children after chronic exposure to mineral oil nose drops and laxatives.⁴ Since then, most cases have been reported in patients with a predisposition to aspiration, such as mental retardation, cleft palate, anatomic or functional abnormality in swallowing.⁴⁻⁸ But, there have been some reports of exogenous LP caused by traditional folk remedies.⁹Various causative agents can cause LP, depending on local life style and cultural differences among patients.^{3,10,11} In China, kerosene, as a special kind of mineral oil for worship, has been reported as a common cause of exogenous LP.^{3,10}

Due to lack of specific radiological features and manifestations of LP and awareness about this disease, diagnosis can be missed or delayed at the right time, which may lead to progress and unnecessary therapy.^{2,12} The nature history and outcome of LP are greatly variable mainly depending on the type, quantity, chemical properties and distribution of inhaled materials and are related to pulmonary tissue injury degree.¹³ At present , the treatment strategy for LP is not well defined in the literature and guildlines, but there is a consensus that the main measure is primarily supportive and generally conservative, and cease to exposure to the lipid substances. In 2020, a systematic review indicated that therapeutic lung lavage might be effective and safe treatment with long-term benefits for exogenous LP.¹² In children patients with diffuse pulmonary lesion, aggressive therapy has been reported.⁷ However, therapy measures about the LP derives largely from case reports and case series, not long-term observational studies.¹² In this study, we evaluated the radiological and clinical features of children LP patients used by therapeutic segmental bronchoalveolar lavage in combination with prednisolone.

2 Methods and Materials

The study was approved by the institutional ethics review committee which waived the requirement for written informed consent because of the nature of the retrospective study.

2.1 Study design

All inpatient children under 18 years of age with a admission diagnosis of ELP and a confirmed history of exogenous oily materials aspiration were retrospectively reviewed from June 2012 to December 2021 from the medical records at First Affiliated Hospital of Guangzhou Medical University, a tertiary care, free-standing public hospital. Medical records were retrospectively reviewed by using a standardized form to collect demographic data, clinical manifestations, laboratory test results and radiological findings. All patients with established ELP were evaluated by the senior attending pediatrician at the inpatient units on the basis of signs, symptoms, and laboratory/imaging findings during hospital stay. The exclusion criterion was suspected with a history of or no evidence of exogenous substances inhalation. A total of 17 children patients was included in the final analysis. CT scans of all children found diffuse pulmonary lesion at admission. Supportive measures, such as oxygen therapy, empirical antibiotic therapy, local or systematic corticosteroids use to slow the inflammatory response, were performed in children with clinical symptoms or severe lung damage. The number of bronchoscopic lung lavage was carried out in terms of the severity of clinical symptoms/signs and radiological findings.

2.2 Data collection

We collected data on demographics (sex, age, weight), symptoms/signs, hospital stay, blood investigations (whole blood count, neutrophil/lymphocyte/monocyte percentage, C reactive protein, procalcitonin, arterial blood gas, peripheral lymphocyte subset percentage), radiological imaging, bronchoalveolar lavage fluid analysis (lymphocyte subset percentage and neutrophil/lymphocyte/macrophage percentage), source of inhaled oil substance, comorbidity, number of therapeutic bronchoalveolar lavage and clinical course. Clinical course was classed into four categories as follows: complete or partial resolution; no change; progression; lost to follow-up. Bronchoscopic data on lymphocyte subset was determined by flow cytometry.

2.3 Radiological imaging's evaluation

High-resolution CT (HRCT) scans of all children were evaluated for the presence and distribution of the following findings: air-space consolidation, ground glass attenuation, crazy-paving pattern, and Poorly defined centrilobular nodules.¹⁴⁻¹⁷ Two investigators independently reviewed the HRCT images, and discrepancies on these findings were discussed by consensus. Criteria for these findings were checked in each patient (Figure 1). Crazy-paving pattern was defined as patchy well-defined areas of ground-glass opacity with superimposed septal thickening.

2.4 Statistical analysis

Data were expressed as medians with interquartile ranges for continuous variables and as numbers with percentages for categorical variables. Among two groups, continuous and categorical variables were compared by using the Mann-Whitney U test and χ^2 test or Fisher's exact test respectively. $P \leq 0.05$ was considered statistically significant. Statistical analysis was carried out by using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, New York) software.

Results

manifestations and radiological features of the children LP patients

In our study, a total of 17 patients were included, with median age of 2 years [Interquartile Range, IQR(1.48~4.23)], in two of which had severe malnutrition and in one of which had obesity, the remaining 14 patients had no risk factors. The most frequent symptoms were cough ($n=14$), fever ($n=14$) and tachypnea ($n=7$). Clinical visit data was available for the 17 children who finally were asymptomatic and

presented normal radiological imagings. One patient taking sewing machine oil for 2 days had a severe pneumothorax, but a good clinical evolution. Corticosteroid and preventive antibiotics use were administered in 12 of the 17 children. Bronchoscopic lavage using normal saline was performed in all children. Characteristics of the patients are listed in the table 1.

Laboratory findings, such as arterial blood gas analysis(ABGA), peripheral blood investigations, bronchoscopic lavage fluid (BALF) analysis and CT features are presented in figure1 and table 2. Mild hypoxemia and hypocapnia were noted. BALF analysis was found in 8 of 17 patients who underwent bronchoscopy, and the increased neutrophilic granulocyte percentage was observed in BALF analysis and peripheral blood investigations.

In most cases, the lesions were multilobular; both lungs were equally involved; the right lung was more extensively involved than the left lung. On CT scan, the most common radiological features in the patients with ELP were bilateral areas of air-space consolidation(15, 93.75%) and poorly defined centrilobular nodules(13, 81.25%). The children had no pleural effusion, lymph-node enlargement or any other chest abnormality. The presence of ground-glass attenuation was observed in 11 cases, and ‘crazy-paving’ pattern(septal thickening) in 6 cases.

3.2 Comparison of two groups from different source of inhaled oily materials

On the basis of aspirated different oily substances, the 17 patients were classed into two groups: mineral oil group and other group. Of those, lamp kerosene was inhaled in 9 cases, machine oil 2 cases, white gas 1 case, butter 1 case, liquid for killing mosquito 2 cases, banana oil 1 case, glue 1 case. The mineral oil group had a significantly higher white blood count than the other group, but no statistical significance. In comparison with the mineral oil group, the other group demonstrated BAL lymphocytosis. The origin of oily materials was no obviously affected in prognosis and laboratory findings of ELP(Table 3).

Discussion

Exogenous lipid pneumonia (ELP) is a rare condition that can be difficult to recognize and results from accumulation of oily materials in the alveoli that are aspirated from vegetable, mineral and animal origins, characterized by lipid-laden macrophages in the sputum or bronchoscopy lavage.^{5,18,19} In the present study, we demonstrated that acute ELP frequently is symptomatic, with respiratory symptoms reported by almost all of affected children patients who had a median 2 years of age. Bilateral areas of consolidative and ground-glass opacities were the most common radiological findings, but crazy-paving pattern on CT scan images was present in less than one-half of affected individuals. Aspirated mineral oil was the most commonly implicated materials. After discontinuation of the causative agent and supportive treatment, such as oxygen therapy, bronchoalveolar lavage and glucocorticoid use, a large percentage of the children patients significantly improved clinically and radiologically. All of the patients had acute ELP in our study, rather than chronic. Pathologically, acute ELP is generally believed to be caused by a foreign body response to fatty substances in the lung lobe,²⁰ therefore, we found that all affected individuals had a markedly higher percentage of neutrophils in BAL fluid and peripheral blood in comparison with the normal range. Acute ELP is more common in the literature report and occurs in association with large-dose inhalation or aspiration in specific clinical settings, such as accidental ingestions in children or fire-eaters, suicide attempts and illegal drug use.^{1,9,13}

The mechanisms by which lipids reach alveoli are aspiration or inhalation, mineral oils enter the respiratory tract without stimulating the cough reflex and impair the mucociliary transport system.¹ Risk factors for ELP include infancy and elderly who usually have anatomic or functional gastroesophageal dysmotility disorder, cleft palate or neuromuscular disorder.⁴ All of children with acute ELP were included in the present study, who had aspirated a large sum of oily materials in an incidental episode and had no other congenital disorders, except the only one malnutrition and two obesity.

In the light of the source of the lipid exposure, lipid pneumonia is generally categorized as the follows: endogenous lipid pneumonia, related to intra-alveolar lipid accumulation as a result from obstruction,

chronic lung infection/disorder, a lipid storage disease; exogenous lipid pneumonia, due to recurrent or accidental aspiration of fatty substances; and idiopathic lipid pneumonia, with no identifiable causative agents or underlying conditions.^{3,11} To precisely review the effect of bronchoalveolar lavage on acute ELP, we only included patients with a confirmed history of aspiration, clinical symptoms and CT scan images, LP is a rarity and, although it's difficult to determine the precise clinical prevalence, autopsy series have reported an incidence of only 1.0%~2.5%.¹³ However, due to lack of specific radiological and clinical features and no awareness of LP, LP is difficult to establish and sometime histopathologic confirmation of the diagnosis may be necessary from respiratory specimens.²¹ Although many of the reports have used lipid-laden macrophage in the sputum or BAL specimen as a diagnostic marker for LP, its specificity and accuracy have been questioned by some researchers.²¹ In the present study, BAL fluid analysis shows the presence of lipid-laden macrophage in the only one case. Therefore, diagnosis of ELP should be based on the triad of history of mineral oil inhalation, compatible radiological imaging, and presence of intra-alveolar lipids and/lipid-laden macrophages.^{4,6,18,20}

BAL is a successful method recommended in the therapy of pulmonary alveolar proteinosis,²²⁻²⁴ but a great many investigations and case-reports have demonstrated good response of whole/segmental lung lavage in the therapy of individuals with LP. In 2020, a systematic review that included 90 ELP patients from 25 case reports and 8 case series studies indicated that therapeutic lung lavage might be an effective and safe therapy with long-term benefits for EL.¹² Whole or segmental BAL is a simple and safe procedure that does not require general anesthesia but cough and hypoxemia may eventually occur during the procedure.²⁴ BAL may result in transient hypoxemia in few children individuals, but it was swiftly corrected by nasal oxygen and, children caregivers did not report any complication after the procedure.²⁵ In our research, all affected children were performed by BAL and had full resolution until the last follow-up, even multiple BAL in some patients on the basis of the clinical-radiological patterns of paediatric ELP.²³ Indeed, it has been reported in the literature that 6 months after ELP diagnosis, untreated children had recurrent respiratory infections that required antibiotic therapy and chest CT pattern still showed areas of ground-glass opacities in the lower lobes and atelectasis.¹¹ BAL is a good strategy recommended in the treatment of paediatric acute ELP in terms of our clinical research.^{25,26}

The development of parenchymal abnormalities in ELP is dependent on the type, amount, frequency, and length of time of inhaled oils. Mineral oil (a mixture of inert, long-chain, saturated hydrocarbons obtained from petroleum) and vegetable-based oils tend to cause minimal to mild inflammatory reactions.^{1,2} The intra-alveolar oils can coalesce in the alveoli and is encapsulated by fibrous tissue, resulting in a nodule or mass (paraffinoma). Conversely, animal fats are hydrolyzed by lung lipases into free fatty acids that trigger a severe inflammatory reaction that manifests as focal edema and intraalveolar hemorrhage.⁶ Fatty acids either remain in the alveolar spaces or are phagocytosed by macrophages that then migrate to the interlobular septa. Regardless of location, the inflammatory response can destroy the alveolar walls and the interstitium, and the resultant fibrosis can occasionally progress to end-stage lung disease.^{18,20,27,28} In this study, we divided all patients into two groups based on the source of aspirated substances, the clinical-radiological features were found no statistical difference in both group.

There are also several limitations in the present study. First, this was a retrospective study conducted in only one hospital so that many confounding factors and various bias could not be avoided due to the inherent nature of the retrospective study. Second, since the affected children were clinically symptomatic in the present study and there was no any other alternative therapy we did not consider it warranted to include a control group of individuals without treatment, so we did not provide significant statistical power to demonstrate the risks and benefits of treatment, especially in radiological aspects. Nonetheless it was possible to establish a comparison with clinic and radiologic features from few children whose parents did not sign the consent for therapeutic BAL, but all parents did approve of aggressive therapy in our study. Third, the radiological findings of all children varied greatly from CT scan images at initial presentation to X-ray films during the follow-up period, therefore, we did not get quantitative data to compare. Finally, the number of children was insufficient to reach a credible and robust conclusion. In the future, larger multicenter prospective cohorts are needed to elucidate the risks and benefits of bronchoscopic lavage and glucocorticoids on children with

ELP.

In conclusion, diagnosis of acute ELP is often difficult. Causative agents of ELP can vary depending on differences in culture and life style of the affected countries and regions. Diagnosis of acute ELP should be based on confirmed exposure to lipid substances and clinical-radiological features. Sufficient exposure data is necessary to reach a diagnosis of acute ELP, and to differentiate it from pneumoconiosis. Therefore, primary preventative measures are essential for protecting these children, and the preventative measures should include increased safety awareness of children's parents or caregivers, appropriately being away from oil-containing substances, children safe health education, and the establishment of an occupational safe education videos for parents.

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Conflict of interest

All of authors declare that they have no conflicts of interest.

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