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Research Article

Investigating the Role of Open Lung Biopsy in Diagnosing the Type of Chronic Lung Disease in Children

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ABSTRACT

Objective: This study was conducted for the practical use of biopsy in the diagnosis of chronic lung disease and the guidance of risks and benefits.

Design of Study: We studied 64 children with chronic lung disease who underwent open lung biopsy in 5 years at the Children's Medical Center.

Results: Biopsy results were diagnostic in 57 cases (89.1%) and non-diagnostic in 7 cases (10.9%). The biopsy determined the type of mass in all cases where a possible diagnosis of lung mass or thoracic wall was made. In 37 cases (57.8%) the diagnosis was changed and the exact diagnosis was determined. The main side effects (including pneumothorax, hemothorax, pyothorax, and pleural effusion) were 50% (32 cases), the most common of which were pneumothorax and pleural effusion, with a total of more than 87% of these major complications. 22 patients (34.4%) required intubation. 24 patients (37.5%) were admitted to the ICU after surgery. The death occurred in only one case, who was a 3-month-old boy with a disorder of INR and suffering from acute respiratory distress syndrome. There was no mortality that could be directly related to surgery.

Conclusion: Open lung biopsy is a gold standard for the histological diagnosis of chronic pulmonary disease in children and plays an important role in the treatment of children with chronic pulmonary diseases. However, serious and common side effects of this method should be considered

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Introduction

Pediatric interstitial lung disease includes a wide range of rare respiratory disorders associated with high morbidity and mortality. The diagnostic approach is based on a combination of assessment, clinical examination, imaging, pulmonary function test, genetic test, Broncho alveolar lavage (BAL), and in most cases lung biopsy. Patients who had a previously known pathology, but the pulmonary symptoms cannot be justified by underlying disease are candidates for screening for pediatric interstitial lung disease [1]. A definitive diagnosis of adult interstitial pulmonary disease is made by CT scan [2, 3]. However, in children, CT scans are usually non-specific and pulmonary biopsies are often required [4, 5]. When non-invasive tests are not enough to diagnose lung disease,

lung biopsy is the gold standard for diagnosing the disease in children with persistent symptoms or worsening clinical condition. Lung biopsy is part of the diagnostic workup for multiple diseases [6], and it is performed for conditions with a high mortality rate. The procedure yields a definitive diagnosis in the majority of cases but infrequently changes therapy [7]. Pediatric surgeons are commonly asked to carry out lung biopsies in children to obtain tissue for definitive histological or microbiological diagnoses [8].

There are several ways to perform a lung biopsy. These include Trans bronchial lung biopsy (TBLB), Trans thoracic lung biopsy (TTLB), Video-assisted thoracoscopic surgery (VATS), and finally open lung biopsy (OLB). Each has its own advantages and disadvantages. Open lung biopsy can help differentiate between reversible and irreversible

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lung diseases and may guide therapy. Histological findings following an open lung biopsy may help clarify the underlying disease and deciding between continuation and withdrawal of ECMO or help in changing other aspects of the treatment [9]. It represents the final necessary step in diagnosis; however, a definitive diagnosis may still remain elusive and medical therapies may not be changed following biopsy [10]. Proceeding with OLB in vulnerable children who already have significant respiratory compromise can often carry significant risk, which needs to be considered when assessing the need for definitive diagnosis [11]. Therefore, careful patient selection is recommended to maximize diagnostic yield [8].

Open lung biopsy is an uncommon procedure in children. Previous reports on the diagnostic use of open lung biopsy have focused on two main groups: Children with undiagnosed lung parenchymal disease who have failed other diagnostic procedures and children with congenital heart disease and pulmonary vascular microanatomy which can provide valuable additional information for cardiac catheterization data [12-15]. The use of open lung biopsy in modern medicine cannot be judged well for several reasons using the available information. Many previous studies have been published more than a decade ago and have been reported before the introduction of current treatment strategies and diagnostic techniques, and the expected mortality spectrum (0% to 62%) and the diagnostic range (9% to 100%), previously reported, is very helpful in selecting criteria for patients who may benefit from this procedure [13, 16]. In addition, in the last decade, the pediatric intensive care unit and the number of immunocompromised children has increased. The diagnostic efficacy of open lung biopsy (57%) and VATS (54%) has been similar, but the morbidity resulting from VATS is clearly lower in terms of surgical duration, pulmonary embolism, and hospital stay [17].

The use of needle biopsy through the skin in combination with HRCT, with a diagnostic efficiency of between 58 and 100% and with low side effects, has been suggested as an alternative to open lung biopsy [5, 18]. But as much as open biopsy, the lungs do not provide stable results [19]. Although trans bronchial biopsy or trans thoracic biopsy has been used successfully in some cases, open lung biopsy (OLB) or video-assisted thoracoscopic surgery (VATS), are the gold standard for providing sufficient tissue for diagnosis. Complications of all types of biopsies include pneumothorax, hemothorax, empyema, atelectasis, pneumonia, etc. Depending on the type and extent of the invasive method, the incidence of each of these complications can be more or less.

Careful consideration should therefore be given to who would benefit most from lung biopsy [6]. Research on the role of OLB in middle and low-income countries is required to guide treatment of children with life-threatening DLD (diffuse lung disease) that does not respond to treatment [20]. Finally, due to the lack of complete knowledge of the subject and the risks of biopsy, as well as the need to perform it in cases where a diagnosis cannot be made for the patient, we decided to examine the role of lung biopsy in the diagnosis of chronic lung disease in children at the Children's Medical Center and by analyzing and reporting the data from our study to describe the role of lung biopsy in diagnosing the type of disease in chronic lung patients.

Methods

This study was a retrospective section and the population we studied on, was all children with chronic pulmonary disease who were referred to the Children's Medical Center Hospital (Children's Scientific Center) in last 5 years and underwent lung biopsy surgery. The criterion for patients to enter the study also included all children with chronic lung disease who were not given a definitive diagnoses of their various disease conditions and were in the age range of 2 months to 16 years, both boys and girls. Also, patients with underlying disease were excluded from the study. Related variables in this study include biopsy complications, post-biopsy mortality and post-biopsy diagnosis, and independent variables including age, sex, coagulation profile, pre-biopsy respiration rate, patient intubation requirement, ICU length of stay, and potential diagnosis Before biopsy, abnormal CXR before biopsy and the type of lung disease.

Each patient's information includes demographic information, information about the disease, the results of tests requested for the patient, therapies performed for the patient, pathology report, complications of pulmonary biopsy that are identified during periodic examinations in patients, and in the patient's clinic file. Other necessary information was entered in the data collection sheets designed to perform this study, according to the data collection sheet.

At the end, the collected information was entered into SPSS v.20 statistical software and analysed. Multivariate linear regression was used to investigate the effect of variables affecting postoperative complications such as age, sex, etc. We also used multivariate linear regression to identify the factors that cause postoperative mortality in children with chronic lung disease.

Results

A total of 64 children with lung disease who needed lung biopsy were included in the study. Patients ranged in age from 2 months to 16 years and averaged 3.5 ± 4.0 years. In terms of gender, 31 boys (47.7%) with an average age of 3.8 ± 4.1 years and 33 girls (50.8%) with an average age of 3.3 ± 4.0 years formed our patients. There was no statistically significant age difference between the sex groups ($p = 0.91$). Among the study subjects, 17 cases (26.6%) did not have Tachypnea, but 47 cases (73.4%) had a high respiratory rate. In terms of coagulation profile, 8 cases (12.5%) had impaired INR (above 1.5) and 10 cases (15.6%) had impaired PTT (above 45 seconds). Major complications (including Pneumothorax, hemothorax, pyothorax, and pleural effusion) occurred in half of the patients (32 individuals) after open lung biopsy. 22 patients (34.4%) required intubation. 24 patients (37.5%) were admitted to the ICU after surgery. the death occurred in only one case, who was a 3-month-old boy with a disorder of INR and suffering from acute respiratory distress syndrome. This patient died after 3 days of hospitalization in the ICU following surgery.

The most common complications in our patients were pneumothorax and pleural effusion, which accounted for more than 87% of major complications. The prevalence of major complications was 41.9% in boys and 57.8% in girls. Fisher's exact test showed no significant statistical dependency between sex and the occurrence of major

complications (p = 0.317). Fisher's exact test did not show a statistically significant dependency between PTT and INR status with the occurrence of major complications after open lung biopsy (p = 0.634 and p = 354, respectively). The highest prevalence of major complications was observed in children under 1 year of age (57.9%) and the lowest

prevalence of major complications was observed in children aged 3 to 6 years (29.4%). Table 1 shows the frequency distribution of all possible preoperative diagnoses. The most common possible diagnosis before lung biopsy was pneumonia. Table 2 shows the frequency distribution of radiographic findings in the studied patients.

Table 1: Frequency distribution of possible pre-biopsy diagnosis.

	Condition	Frequency	Percentage
Preoperative diagnosis	Mass	5	7.8
	Cavity damage	6	9.4
	Pulmonary HTN	2	3.1
	Pneumonia	27	42.2
	External object	2	3.1
	No diagnosis	14	21.9
	Other	8	12.5
	Total	64	100.0

Table 2: Frequency distribution of radiographic findings in the studied patients.

	Condition	Frequency	Percentage
Radiographic findings	Not reported	20	31.3
	Mass	9	14.1
	Cyst	3	4.7
	Emphysema	3	4.7
	Consolidation	16	25.0
	Effusion	6	9.4
	Pneumothorax	5	7.8
	Other	2	3.1
	Total	64	100.0

Biopsy results were diagnostic in 57 cases (89.1%) and non-diagnostic in 7 cases (10.9%). In 13 cases which the probable diagnosis was unclear, 11 cases were confirmed after biopsy, but in 2 of these 13 cases was undiagnosed. Biopsy determined the type of mass in all cases, which

a possible diagnosis of lung mass or thoracic wall was made. In 37 cases (57.8%) the diagnosis was changed and the exact diagnosis was made. Table 3 shows all the diagnoses before and after lung biopsy in our study.

Table 3: Diagnosis before and after open lung biopsy.

Row	Preoperative diagnosis	Postoperative diagnosis	Row	Preoperative diagnosis	Postoperative diagnosis
33	Pneumonia	Neuroblastoma	1	Pulmonary mass	Wilms metastatic mass
34	Pneumonia	Inflammatory pulmonary necrosis	2	Thoracic wall mass	Capillary hemangiomas
35	Unknown	Inflammatory pulmonary necrosis	3	Simple lung cyst	Hydatid cyst
36	Pneumonia	Inflammatory pulmonary necrosis	4	Pulmonary hypertension	Bronchiolitis Obliterans
37	Pneumonia	Pulmonary tuberculosis	5	Pneumonia	Fibroconnective tissue & congestion
38	Swallowing an external object	External object	6	Pneumonia	Necrosis due to pneumonia
39	ALL with respiratory distress	Normal	7	Unknown	Lobar emphysema
40	AML & H1N1	Metastasis of leukemic	8	Cystic adenomatous malformation	Cystic adenomatous malformation
41	Hemophagocytosis syndrome	Hemophagocytosis syndrome	9	Hydatid cyst	Hydatid cyst
42	DIC syndrome	Hemophagocytosis syndrome	10	Emphysema	Atelectasis and emphysema
43	Pulmonary hypertension	Normal	11	Pneumonia	ILD
44	Pneumonia	ILD	12	Pneumonia	Granulation tissue
45	Reserve disease	Normal	13	Pneumonia	Inflammatory pulmonary necrosis
46	Hepatic encephalopathy	Reserve disease	14	Pneumonia	Cystic adenomatous malformation
47	Gastroenteritis	ILD	15	Chronic pneumonia	ARDS
48	Metabolic disease	ILD	16	Pneumonia	ILD
49	Pneumonia	Pulmonary tuberculosis	17	Pneumonia	ILD

50	Pneumonia	Lung alveolar destruction	18	Unknown	ILD
51	Lupus	Normal	19	Unknown	Pulmonary vasculitis
52	ARDS	ILD	20	Pneumonia	Liver metastasis
53	Pneumonia	ILD	21	Lung tumor	Neuroblastoma
54	Unknown	Normal	22	Pneumonia	ILD
55	Unknown	ILD	23	Pneumothorax	Lobar emphysema
56	Pneumothorax	Lobar emphysema	24	Unknown	Cystic adenomatous malformation
57	External object	Pneumonic aspiration	25	Pneumonia	ILD
58	Pneumonia	Alveolar destruction of the lungs and ARDS	26	Pneumonia	Pulmonary tuberculosis
59	Hyper IgM	ILD	27	Unknown	Askin tumor
60	Pneumonia	Pulmonary tuberculosis	28	Unknown	ILD
61	Unknown	Normal	29	Pneumonia	Neuroblastoma
62	Pneumonia	Pneumonic aspiration	30	Pneumonia	Actinomycin pneumonia
63	Pneumonia	ILD	31	Unknown	Histiocytosis X
64	Unknown	Neuroblastoma	32	Unknown	Spindle cell tumor

Discussion

The necessity for tissue biopsy should be critical to establishing a diagnosis, however, its indications and diagnostic utility remain unclear [10]. We reported the results of the 5-year experience of surgeons at the Pediatric Medical Center, with open lung biopsies. Our primary goal was to determine the diagnostic efficacy of open lung biopsy and to determine its complications. Open lung biopsy was diagnostic in 89.1% and non-diagnostic in 10.9%. Also, out of 13 cases without initial diagnosis, the histological sample obtained from open lung biopsy was diagnostic in 11 cases. The diagnosis was altered in 57.8% of cases, or a more accurate diagnosis was made, and treatment changed somewhat. The collections, which the results of them have been reported by Davies *et al.*, Coren *et al.*, and Greenhalgh *et al.*, are the most comparable studies performed prior to this study in terms of size, study population,

and surgical procedure used in our study [21-23]. These 4 studies are also similar in terms of diagnostic diversity (although in Davies *et al.*'s study, the prevalence of immunodeficiency and infections was higher).

Table 4 compares the findings of our study in terms of diagnostic efficiency, treatment change, complication rate and mortality rate with the other 6 studies conducted before our study. The mortality in our study was similar to the results of studies by Neuhaus *et al.*, Coren *et al.* and Chan *et al.*, but the complication in our study was similar to that of Davies *et al.*, which the complication occurred in half of the cases [22-25]. This complication is one of the highest among similar studies. The diagnostic efficiency of our study (89.1%) and the change in treatment in our study (57.8%) was close to the results of previous studies. Among the similar studies listed in (Table 4), our study had the largest sample size after the study of Neuhaus *et al.* performed on 121 patients [24].

Table 4: Comparison of data from previous studies with the present study.

	Change in treatment (%)	Histological diagnosis (%)	Mortality rate (%)	Complications (%)	Number of patients	Year
Davies <i>et al.</i> [22]	-	64	24	51	47	1997
Neuhaus <i>et al.</i> [24]	-	95	5	28	121	1997
Steinberg <i>et al.</i> [26]	69	96	38	8	26	1998
Coren <i>et al.</i> [23]	56	93	0	11	27	1999
Chan <i>et al.</i> [25]	83	100	0	25	12	2003
Greenhalgh <i>et al.</i> [21]	48	79	12	24	33	2013
Current study	57	89	1/5	50	64	2015

Table 5: Comparison of data from the present study with other studies.

The authors	Date	Number of patients	Complications rate (%)	Mortality rate (%)	Histological diagnosis (%)	Change in treatment (%)
Current study	2015	64	50	1/5	89	57
Lamoshi <i>et al.</i> [7]	2015	99	-	25	71	16
Houmes <i>et al.</i> [9]	2016	25	0	0	88	48
Gie <i>et al.</i> [20]	2017	51	12	0	86	33
Sobrinho <i>et al.</i> [6]	2018	37	16	10	62	43
Hafezi <i>et al.</i> [10]	2019	19	0	-	63	63
Chan <i>et al.</i> [8]	2019	39	2.5	0	64	38
Sinha <i>et al.</i> [11]	2019	42	24	0	79	52

Table 5 also compares the results of our study with seven other studies. The diagnostic efficiency of our study is similar to that of Homs *et al.* and Gay *et al.* Also, in terms of changing the treatment, it is similar to the studies performed by Hafezi *et al.* and Sina *et al.* The mortality rate in our study was similar to that studied by Chan *et al.*, Sinha *et al.*, Gie *et al.*, Houmes *et al.*, but in terms of the rate of complication, our study was not comparable to these studies and had the highest rate of complication.

It should be noted that the authors who reported a higher diagnostic percentage were from non-regional respiratory centers with higher experience and expertise in histological services. Although there have been changes in treatment in about half of the cases, this should not be construed to mean that half of the biopsies were unnecessary. Confirmation of the diagnosis can be as beneficial as a change in diagnosis, as it builds confidence in continuing the course of treatment, which is associated with serious side effects and also allows families to explain the process of possible progression and prognosis of the disease. Despite such benefits, a biopsy should not be used to confirm diagnoses that have previously been diagnosed with reasonable certainty. The results of our study showed that this complication after open lung biopsy is associated with the need for postoperative intubation as well as hospitalization in the ICU. As a result, efforts to reduce the complications of biopsy appear to lead to shorter hospitalization in hospital and intensive care units and reduce health care costs for these patients. Histological diagnosis is essential in determining the treatment of this group of children. Lung biopsy is useful in many cases, and by providing a sample of tissue, it helps to definitively diagnose the disease, which in many cases can manage and change the patient's diagnostic and treatment program.

Open lung biopsy under general anaesthesia plays an important role in the treatment of children with chronic pulmonary disease. However, serious and common side effects of this method should be considered. The Complications occurred in half of our study subjects and mortality occurred in one case of total patients (1.5% mortality) in our study. There was no mortality that could be directly related to surgery. According to the report of the most serious complications after biopsy in the present study compared to previous studies, it seems that review of techniques used during open lung biopsy and postoperative care is required. It is important to minimize the risk of failure in clear diagnosis to avoid multiple procedures under general anaesthesia. Open lung biopsy is still the gold standard for histological diagnosis of unknown chronic pulmonary disease in children.

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