Original Article

Is It Better to Operate Congenital Lung Malformations when Patients are Still Asymptomatic?

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Abstract

Context: Congenital lung malformation (CLM) is a rare developmental anomaly of the lower respiratory tract. The purposes are to define if the presence of respiratory symptoms, in CLM may affect surgical outcomes and to define optimal timing for surgery in asymptomatic patients.

Settings and Design: Retrospective review of patients with CLM from 2004 to 2018. Asymptomatic and symptomatic patients were compared. Moreover, asymptomatic patients were stratified according to age at surgery (< or >6 months).

Subjects and Methods: Demographic data, prenatal diagnosis, symptoms, CLM's characteristics, operative and postoperative data were collected. Patients were divided into two groups based on the presence or none of respiratory symptoms.

Statistical Analysis: Data were compared using the Fisher's exact test for qualitative values and Mann-Whitney test for quantitative values $P < 0.05$ was statistically significant.

Results: One hundred and eighty-six patients were treated. Asymptomatic were 137 (74%), while symptomatic were 49 (26%). The most common presenting symptoms were respiratory distress (n = 30, 61%) followed by pneumonia (n = 18, 38%). Prenatal diagnosis of CLM was performed in 98% of asymptomatic patients compared to 30% of symptomatic (P = 0.001). Surgical excision was performed in all cases, and in 50% by thoracoscopy, without difference between the two groups. In 97% of all cases, a lung sparing surgery was performed without difference between the groups. Symptoms are significantly associated with older age, location in the upper lobe, and lobar emphysema. Length of stay in intensive care, postoperative complications, and reintervention rate were higher in the symptomatic group. Eighty-one asymptomatic patients underwent surgery <6 months of life; they had a lower rate of surgical complications (2%) compared with those >6 months (7%).

Conclusions: The present study describes a comprehensive picture of CLM. In addition, we emphasize the role of early postnatal management and thoracoscopic surgery, also before 6 months of life, to prevent the onset of symptoms that are associated with worse outcomes.

Keywords: *Congenital lung malformation, congenital pulmonary airway malformation, lung-sparing surgery, thoracoscopy*

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Introduction

Congenital lung malformation (CLM) is a rare developmental malformation of the lower respiratory tract.[1-4] CLMs include a wide spectrum of diseases

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such as: (i) congenital pulmonary airway malformation (CPAM), (ii) bronchopulmonary sequestration, (iii) hybrid lesions (contain elements of CPAM and bronchopulmonary sequestration), and (iv) bronchogenic or foregut cysts, bronchial atresia, and congenital lobar emphysema.[2,3,5-8]

The proper management for CLMs is still unclear in particular concerning indications and timing for surgery.[9-13]

Our purpose was to review our experience with CLM emphasizing natural history, management and outcome by comparing patients who were asymptomatic with those who were symptomatic at the time of surgery. Moreover, we focused on the age at surgery (early <6 months, vs. late >6 months) in asymptomatic patients to verify if it may have any impact on the patient's outcome.

Subjects and Methods

This is a retrospective review of children with CLMs, referred to our pediatric surgery department between January 2004 and October 2018.

Patients were divided into two groups based on the presence or none of respiratory symptoms before the operation: Group I included asymptomatic children, whereas symptomatic children were included in Group II. Data collected from the charts included patient's characteristics defined as prenatal diagnosis (and mean gestational age at diagnosis), sex, age and weight at operation, preoperative symptoms (defined as pneumonia, respiratory distress, pneumothorax, etc.), and associated malformations. CLM's radiological characteristics, derived from computed tomography (CT-scan), magnetic resonance imaging (MRI) or Visible Patient™ three-dimensional reconstruction, were defined as: diameter, laterality, and location of CPAM in either upper, middle, or lower lobes of the lung. Operation-related variables included the duration of procedure in minutes, type of lung surgical (LS) resection performed defined as segmentectomy or wedge resection, intra-operative complications, and the need for conversion to thoracotomy. Postoperative variables included duration of postoperative pleural drain, length of stay in the intensive care unit, length of hospital stay in days, histological findings of CLM, postoperative complications (defined as pneumonia, persistent pneumothorax, respiratory distress, pleural effusion, and asthma), and re-intervention. All patients were followed up with regular clinical monitoring (outpatient clinic visit at the 1st, 6th, and every 12th month) as well as radiological evaluation (chest radiography 3 and 12 months after the operation). Postoperative CT scan was performed only in case of symptoms or persistence of abnormalities on the plain X-ray, and at least 12 weeks after surgery.

Furthermore, asymptomatic children were stratified according to age at surgery to verify if it may affect their outcome. A cutoff of 6 months of age was established because patients younger than that are generally considered at increased risk of perioperative complications.

Statistical analysis was performed using the GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com. The bivariate analysis involved the Mann-Whitney U (Wilcoxon rank-sum) test for continuous variables with nonparametric distribution and 2 × 2 contingency tables and the Fisher's exact test for categorical variables. $P < 0.05$ was considered statistically significant.

Results

One hundred and eighty-six patients were consecutively treated from January 2004 to October 2018. One hundred and thirty-seven were included in the asymptomatic group, whereas 49 were included in the symptomatic group.

Clinical data, CLM's characteristics, operative and outcome data are reported in Table 1. All fetuses were regularly followed with at least one ultrasonography. Prenatal diagnosis of pulmonary malformations was made in 149 cases (80%). However, the rate of prenatal ultrasonographic detection of CLM was consistently higher in the symptomatic group compared to asymptomatic, 137 (74%) versus 49 (26%) ($P = 0.001$), respectively. All cases were monitored during pregnancy by ultrasound and fetal-MRI revealing stability in volume and size in 178 cases (96%).

For Group I patients, there were 78 males and 59 females with a mean age at birth of 36.5 ± 4.8 weeks. According to our protocol, all cases were studied by chest X-ray within 24/48 hours after birth and by chest CT within 3 months of age. More recently, chest-MRI has been introduced as the first radiological study during the 1st month of life in substitution of CT scan. All confirmed lesions were evaluated by CT scan and scheduled for surgery within the 1st year of age. Mean age at the time of surgery was 11.8 ± 27.81 mo [Figure 1].

For Group II patients, there were 29 males and 20 females with a mean age at first presenting symptoms of 50.4 ± 60 months. Symptoms onset was observed within the 1st month of life in 11 cases (22%). Among those patients, pneumonia was observed in 37%

Table 1: Patients', congenital lung malformation, operative and postopertative characteristics, divided into two groups, asymptomatic versus symptomatic

	Asymptomatic=137 (%)	Symptomatic=49 (%)	*P*
Patients'characteristics			
Prenatal diagnosis	134 (98)	15 (31)	0.001
Age at surgery (mean±SD)	11.8±27.81 mo	58.83±67.3 mo	0.001
Weight at surgery (mean±SD)	10.2±6.6 kgs	14.8±12.4 kgs	0.86
Symptoms			
Pneumonia		18 (37)	
Respiratory distress		15 (30)	
Pneumothorax		10 (20)	
Thoracic pain		6 (13)	
Associated malformations	12 (9)	6 (12)	0.57
CPAM characteristics			
Laterality			
Right	71 (52)	22 (45)	0.50
Left	68 (49) (two bilateral)	27 (55)	0.50
Location			
Upper	36 (26)	22 (43)	0.03
Middle	8 (6)	8 (14)	0.06
Lower	101 (74)	20 (39)	0.001
Multi-lobar	8 (6)	1 (2)	0.67
Diameter (mean±SD)	4.5±2.5 cms	4.9±2 cms	0.44
Histology			
CCAM	65 (47)	17 (35)	0.13
Hybrid lesions	6 (4)	0	0.34
Intralobar Sequestration	35 (25)	9 (18)	0.33
Extralobar Sequestration	20 (14)	3 (6)	0.13
Bronchogenic cyst	1 (1)	2 (5)	0.17
Lobar emphysema	22 (16)	15 (30)	0.03
Operative data			
Surgical technique			
Thoracotomy	76 (55)	28 (57)	0.86
Thoracoscopy	61 (45)	21 (43)	0.86
Duration of procedure (mean±SD)	105.1±43.5 min	116.8±52.8 min	0.11
Type of procedure			
Lobectomy	5 (4)	2 (4)	1.00
Segmentectomy	8 (6)	2 (4)	1.00
Wedge resection	114 (83)	40 (82)	0.82
Others	10 (7)	5 (10)	0.47
Postoperative data			
Duration of postoperative drainage	6.0±5 days	6.2±4.5 days	0.80
Days in intensive care	3.1±2.5 days	7.0±14 days	0.002
Length of hospital stay	13.9±15.1 days	19.2±23 days	0.07
Duration of follow-up (mean±SD)	30.7±32.4 mo	21.6±22.1 mo	0.07
Postoperative complications	10 (7)	10 (20)	0.32
Pneumonia	3 (2)	4 (8)	0.01
Persistent pneumothorasx	4 (3)	4 (8)	0.21
Respiratory distress	3 (2)	2 (4)	0.60
Reintervention	0	3 (6)	0.01

P<0.05 was considered as statistically significant. CPAM: Congenital pulmonary airway malformation, SD: Standard deviation

of cases followed by respiratory distress in 30%. All cases were primarily studied by chest X-ray and those with suspected images for lung lesion or persistent pneumothorax or severe respiratory compromise underwent a CT chest scan. After symptoms resolution, all cases were addressed to surgery. Comparing the two groups for lesion's characteristics, we observed that CLMs were more commonly located in the

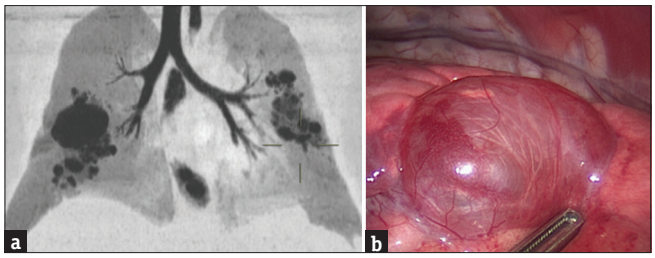

Figure 1: (a) Computed tomography coronal scan showing multiple complex congenital lung malformations involving both lungs in the middle and the basal segments of the lower right lobe and the lower left lobe. (b) Intraoperative findings of the left lung congenital lung malformation, all lesions were treated by lung-sparing surgery

upper lobe (P = 0.03) and were larger (P = 0.05) in symptomatic compared with asymptomatic. Concerning histological analysis, we observed that lobar emphysema had higher prevalence in Group II compared with Group I, 30% versus 16%, P = 0.03, respectively. Surgical details are reported in Table 1. The surgical approach was decided according to patient's conditions and surgeon's preference. Ninety-six percent of patients underwent lung-sparing surgery without difference between the two groups. Mean operative time was slightly longer for symptomatic patients compared with asymptomatic patients (116.8 ± 52.8 min vs. 105.1 ± 43.5 min, P = 0.11). A postoperative pleural drain was placed in all patients with a mean of 6.1 ± 5 days, without difference between the two groups (P = 0.80). The length of stay in intensive care was longer in symptomatic children (P = 0.002). The mean length of hospital stay was 15.5 ± 12 days without difference between the two groups. The overall rate of postoperative complications was slightly higher in Group II (n = 10, 20%) compared to Group I (n = 10, 7%), P = 0.32. Surgical reintervention was required in three cases, and all of them belonged to the symptomatic group, in 2 for persistent pneumothorax, while in one for respiratory distress due to bronchopleural fistula. Patients in the asymptomatic group were subsequently stratified according to age at time of intervention (< or >6 months). Data are shown in Table 2. Eighty-one patients, among asymptomatic CLM, underwent surgery before 6 months of life, while 56 were older than 6 months. The two groups presented differences concerning the rate of prenatal diagnosis, age and weight at the time of surgery. However, no difference was found among these two groups concerning CLM's characteristics, operative and postoperative data. The rate of postsurgical complications was slightly higher in patients younger than 6 months, but is considered as not being quite statistically significant (7% vs. 2%, P = 0.24, respectively).

Discussion

CLMs are a group of heterogeneous developmental malformations that involves the lower respiratory tract. Despite its rarity, CLMs represent the most common congenital lung lesions.[4,14-17] The debate concerning the proper postnatal management of CLMs is still open, and it is focusing on the indication and timing for surgery in these children.[2,16,18-22]

Herein, we report our single-center experience in managing CLMs focusing on the differences between asymptomatic and symptomatic patients. Based on our cohort of 186 cases of CLM, we observed that surgical resection, in asymptomatic children, is associated with: faster procedure, shorter length of stay in the intensive care unit and lower rate of postoperative complications.

Recently, consistent improvements in prenatal diagnosis, such as the use of magnetic MRI, have improved sensitivity and specificity in detecting CLM.[6,23-25] Most of the babies affected by CLMs have a good perinatal outcome; however, a minority of these lesions may complicate with fetal hydrops or require urgent surgery after birth. Consequently, in all cases of suspected CLM, a planned delivery in a tertiary care center is recommended.

Although the management of children with symptomatic CLMs is reasonably straightforward, there is an ongoing debate regarding the need for and timing of surgical intervention in children with asymptomatic lesions.[20-22] The risk of developing respiratory symptoms such as pneumonias, spontaneous pneumothorax or respiratory distress, is estimated at 38% of prenatally identified CLM.[26] The age at symptoms onset may range from neonatal period to adulthood.[27] In our series, among 186 cases of CLM, clinical symptoms were recorded in 49 cases (26%) varying from recurrent pneumonia (37%) and respiratory distress (30%), with a mean age at the time of presentation of 4.8 ± 5 years. In our cohort, we observed that symptomatic patients had a worse outcome (longer hospitalization in the intensive care unit and higher rate of postoperative complications) compared with asymptomatic patients. In accordance, Conforti *et al*. reported that infants affected by CLMs operated on when asymptomatic underwent faster mechanical ventilation, shorter pleural drainage stay, and hospitalization compared with symptomatic patients.[21] Furthermore, Stanton *et al*. confirmed that the risk of developing a postoperative complication when surgery was carried out while the patient was symptomatic increased >2-fold compared with asymptomatic patients.[28] Some of pulmonary complications may require surgical re-intervention. In our cohort, three

Table 2: Asymptomatic patients', congenital lung malformation, operative and postoperative characteristics, stratified into two groups based on the age at surgery; before and after 6 months of age *P*<0.05 was considered as statistically significant

	<6 months *n*=81 (%)	>6 months *n*=56 (%)	*P*
Patients' characteristics			
Prenatal diagnosis	81 (100)	51 (91)	0.01
Sex (male/fenale)	38/43	30/26	-
Age at surgery (mean±SD)	4.14±2.08 months	7.66±9.35 months	0.009
Weight at surgery (mean±SD)	6.21±1.48 kg	7.51±2.39 kg	0.001
Associated malformations	4 (5)	5 (9)	0.48
CLM characteristics			
Diameter (mean±SD)	4.07±1.51 cm	4.23±1.66 cm	0.55
Histology			
CCAM	42 (52)	21 (37.5)	0.11
Hybrid lesions	2 (2)	3 (5)	0.39
Intralobar Sequestration	20 (25)	17 (31)	0.55
Extralobar Sequestration	13 (16)	5 (9)	0.30
Bronchogenic cyst	0	3 (5)	0.06
Lobar emphysema	4 (5)	7 (12.5)	0.10
Operative data			
Surgical technique			
Thoracotomy	44 (54)	28 (50)	0.72
Thoracoscopy	37 (46)	28 (50)	0.72
Duration of procedure (mean±SD)	106.33±36.1 min	106.0±36.5 min	0.95
Type of procedure			
Lobectomy	3 (4)	0	0.06
Segmentectomy	4 (5)	2 (3.5)	1.00
Wedge resection	61 (75)	48 (86)	0.19
Others	13 (16)	6 (10.5)	0.45
Postoperative data			
Duration of postoperative drainage	6.0±5 days	5.9±4.8 days	0.90
Days in intensive care	3.4±2.9 days	3.1±2.4 days	0.52
Length of hospital stay	14.1±11.6 days	12.0±9.7 days	0.26
Postoperative complications	6 (7)	1 (2)	0.24
Pneumonia	0	0	-
Persistent pneumothorax	4 (5)	1 (2)	0.64
Respiratory distress	0	0	-
Others	2 (3)	0	0.51
Reintervention	1 (1)	0	1.00

CLM: Congenital lung malformation, CPAM: Congenital pulmonary airway malformation, SD: Standard deviation

patients required surgical re-intervention; all of them belonged to symptomatic group. In our opinion, it was because lung margins are more difficult to seal in the context of inflamed tissue. Moreover, anatomical margins of CLM could be altered after chronic inflammation increasing the risk of positive margins.

The debate on best timing for surgery in asymptomatic CLM is still ongoing. Interestingly, Calvert and Lakhoo, in their series of 19 patients, reported a higher incidence of chronic inflammation on the histologic examination in children treated at 6 months or older.[29] Increased rate of inflammation and infection over time render the surgery more difficult after months or years of evolution.[2] Furthermore, the lung maintains the capacity to expand and develop until 4 years of age allowing better compensation when early surgery is performed.[13] Eber reported that best timing seems to be between 6 months and 2 years of age because anesthetic and surgical risks decrease after the first months of life.[30] Furthermore, other authors suggest that surgery within the third or 4th month of age is safe and effective and is associated with less pulmonary tissue inflammation.[21,27] Our internal CLM's protocol management for asymptomatic babies suggests to perform surgical resection within the 1st year of life. This allows us to reduce the risks related to general anesthesiology and safely perform minimally invasive surgery by thoracoscopy keeping rate of postoperative complications below 7%. Moreover, surgery performed under 6 months of age does not negatively affect the surgical and post-operative outcome.

Regarding CLM, we observed that 30% of symptomatic patients had a lobar emphysema; this could be explained by the defective structure of the bronchial tree and the anomalous air drainage that are predisposing for developing pulmonary infection.

Many surgical options have been proposed in the treatment of CLMs such as anatomical segmentectomy, wedge resection, lobectomy, or pneumonectomy.[12,28] Recently, the thoracoscopic approach is replacing thoracotomy even in small infants. Nowadays, many authors, and our center too, have advocated a tailor-suited surgical approach for each patient by introducing lung-sparing techniques.[5,12,30,31] Recent studies have also demonstrated that lung-sparing surgery is as effective as lobectomy regarding risks of leaving residual disease or recurrence. Furthermore, this approach is very appealing because it allows to preserve normal lung parenchyma and improve clinical outcome.[5,30] In our institution, since 2001, the lung-sparing technique has been employed for smaller, well-defined segmental lesions and in children with bilateral or multi-lobar disease. During these years we have built up solid experience in performing lung-sparing surgery via thoracoscopy. In our institution, since its first description, lung-sparing surgery was routinely performed in patients with both asymptomatic and symptomatic CPAM, despite their age. We believe that this is the result of an accurate preoperative multi-plane CT reconstruction of the lesion. This is mandatory for a proper resection: this anatomical reconstruction allowed us to assess the lesion along the whole surface of the lung, delineating the anatomy of the lung and of the malformation and supporting its resection. Potential limitations for lung-sparing surgery could be considered: CLM location in the lower lobe and lesion diameter >5 cm. Both can be reduce visibility mobilization of the lung during procedure.

In our cohort, we did not observe any difference between the two groups concerning surgical approach (thoracoscopy or thoracotomy), conversion rate, and surgical technique (lobectomy or lung sparing resection). These data demonstrate that despite lung infection may compromise lung anatomy or complicate with empyema, thoracoscopy can nevertheless be a feasible surgical approach. Furthermore, the absence of malformation residuals on margin resection in both groups underlines how this technique, following a very detailed anatomical study of patients, is a safe choice for the treatment of lung malformations.

Conclusions

In conclusion, we emphasize the role of early postnatal management to prevent the onset of symptoms that are associated with poorer outcome. It is crucial, for fetuses with prenatal finding of CLM, to plan delivery in a hospital with neonatal intensive care and pediatric surgery. Finally, we demonstrate the safety and the feasibility of the innovative lung-sparing surgical technique without increasing the risk of CLM residuals and improving postoperative outcomes.

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Conflicts of interest

There are no conflicts of interest.

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