Respiratory Morbidity in Infants Born With a Congenital Lung Malformation

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abstract

BACKGROUND AND OBJECTIVES: The actual frequency of respiratory symptoms related to congenital pulmonary malformations (CPMs) remains undetermined. The goal of this study was to prospectively evaluate the respiratory symptoms occurring in infants with prenatally diagnosed CPMs, identify factors associated with the occurrence of these symptoms, and evaluate their resolution after surgery.

METHODS: Infectious and noninfectious respiratory symptoms were prospectively collected in a French multicenter cohort of children with CPMs.

RESULTS: Eighty-five children were followed up to the mean age of 2.1 ± 0.4 years. Six children (7%) underwent surgery during the first 28 days of life. Of the 79 remaining children, 33 (42%) had respiratory symptoms during infancy before any surgery. Wheezing was the dominant symptom (24 of 79 [30%]), and only 1 infant had documented infection of the cystic lobe. Symptoms were more frequent in children with noncystic CPMs, prenatally ($P = .01$) or postnatally ($P < .03$), and with postnatally hyperlucent CPMs ($P < .01$). Sixty-six children underwent surgery during the follow-up period, and 40% of them displayed symptoms after the intervention. Six children had documented pneumonia during the postoperative period. At the end of the follow-up, pectus excavatum was observed in 10 children, significantly associated with thoracotomy ($P < .02$) or with surgery before the age of 6 months ($P < .002$).

CONCLUSIONS: CPMs are frequently associated with wheezing episodes. Surgery had no significant impact on these symptoms but was associated with a paradoxical increase in pulmonary infections, as well as an increased risk of pectus excavatum after thoracotomy.

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WHAT'S KNOWN ON THIS SUBJECT: Poor knowledge regarding the natural history of congenital pulmonary malformations (CPMs) hampers standardized prenatal and postnatal care, with most decisions, including those relating to the need for the surgical removal of asymptomatic malformations, highly dependent on the physician.

WHAT THIS STUDY ADDS: Infants with CPMs had a low rate of infection but a high rate of wheezing episodes, especially when CPMs had a hyperlucent appearance. Surgery had no impact on wheezing prevalence. Our results support a conservative management for noncystic malformations.

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Abnormal lung morphogenesis leads to a spectrum of congenital pulmonary malformations (CPMs), including congenital cystic adenomatoid malformations (CCAMs), sequestrations, bronchial atresia, congenital lobar emphysema, and bronchogenic cysts, which may have pathogenic mechanisms in common.[1] Our poor understanding of these malformations hampers standardized prenatal and postnatal care, with most decisions, including those related to the need for the surgical removal of asymptomatic malformations, highly dependent on the physician.[2,3]

The prevention of infection is often offered as an argument for systematic surgical removal, particularly because surgery is believed to become more difficult once infection has occurred.[4] The actual frequency of respiratory symptoms related to CPMs remains undetermined. In a systematic review, >15% of children with CPMs required emergency surgery for symptoms at a median age of 56 months. By contrast, recent data from the Southampton retrospective cohort suggest that the risk of spontaneous complications within the first 5 years of life is actually much lower than generally believed, calling into question the justification of the systematic surgical removal of these malformations to prevent complications.[5] In this cohort, 92% of children who were asymptomatic as neonates could be conservatively managed until the end of follow-up; pneumonia within the cystic lobe was observed in only 3% of children. However, no information was available regarding the occurrence of noninfectious complications, such as wheezy exacerbations, in these infants. It was recently suggested that children undergoing surgery for CPMs had a significantly higher prevalence of wheezing and a greater need for bronchodilators.[6] However, no multicenter study prospectively evaluating respiratory morbidity in children with prenatally diagnosed CPM has ever been performed. A prospective national database for children with CPMs has been created in France.[7]

In the present study, the respiratory symptoms occurring in infants with prenatally diagnosed CPMs were evaluated to identify factors associated with the occurrence of these symptoms and to assess their resolution after surgery.

METHODS

Study Design

The French RespiRare database for rare respiratory diseases in children was established to record extensive information for all forms of rare pediatric lung diseases, including CPMs. A complete description of this database has been published elsewhere.[8] The database and data collection methods were approved by the French national data protection authorities, the "Commission Nationale de l'Informatique et des Libertés" and the "Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé." Informed consent is obtained from parents before the inclusion of data for their children in the database. The first results from this database to be published were related to neonatal findings for infants with malformations.[7] We extracted the files of patients born between December 2008 and January 2012 with a prenatal diagnosis of hyperechoic and/or cystic lung lesions from this database. A total of 85 patients from 11 centers were identified. The present study was approved by the institutional review board of the French Respiratory Society (CEPRO 2016-009).

Follow-up of Children With CPMs

In France, there are no national guidelines for the management of children born with a CPM. Reference centers have been established throughout the country, and national efforts are being made to collect standardized data prospectively for all affected children (ie, the RespiRare database), but management decisions differ between centers. In particular, decisions concerning the surgical excision of asymptomatic lesions vary between centers. All French centers currently remove macrocystic malformations systematically, but some adopt conservative approaches for noncystic malformations; others offer the elective surgical removal of all malformations. The frequency of consultations also differs between centers, but the same parameters are recorded at each visit. All children undergo assessment between the ages of 2 and 3 years.

Data Collection

The following data were extracted from the database: prenatal morphologic appearance of the lesion, including its size, location, and type; associated prenatal abnormalities, such as mediastinal shift, polyhydramnios (defined as an amniotic fluid index greater than the 90th centile for gestational age), or hydrops; gestational age at delivery and birth weight; neonatal respiratory status; wheezing episodes diagnosed by a physician within the first 2 years of life; lower respiratory tract infection (with chest radiograph documentation); admission to the hospital within the first 2 years of life; and surgical removal of the malformation. Height and weight are expressed as SD scores relative to the French reference curves.[9] Growth failure was defined as the loss of 1 SD from the growth curve at 2 consecutive consultations.

Statistical Analysis

In the primary analysis, infants with no respiratory symptoms

(wheezing and/or lower respiratory tract infection) were compared with those displaying respiratory symptoms. In the secondary analysis, factors associated with symptom occurrence in children with CPMs were evaluated. Analysis of variance was used to compare continuous variables between groups. Quantitative data are presented as mean ± SD or observed number/total number (%). Qualitative variables, expressed as percentages, were compared in χ^2 tests or Fisher's exact test (if <5 infants in 1 group). $P < 0.05$ was considered to indicate a statistically significant difference.

TABLE 1 Characteristics of the Population ($N = 85$)

Prenatal and Postnatal Characteristics	*n/N* (%) or Mean ± SD
Appearance on prenatal ultrasound	
No cyst (hyperechoic)	25/85 (29)
Presence of cyst(s)	60/85 (71)
Right-sided malformation	46/85 (54)
Prenatal systemic vascular supply	16/82 (20)
Prenatal compression	
Mediastinal shift	28/81 (35)
Polyhydramnios and/or ascites	10/81 (12)
Gestational age at birth, wk, $n = 85$	39.0 ± 1.7
Birth weight, g, $n = 85$	3247 ± 518
Respiratory symptoms at birth	
Any sign	19/85 (22)
With oxygen requirement	12/85 (14)
Associated malformations at birth	
Heart	4/84 (5)
Kidney	6/84 (7)
Pectus excavatum	3/84 (4)

RESULTS

Eighty-five children with prenatal diagnoses of CPM were followed up prospectively. The final diagnosis, obtained by using a postoperative pathologic examination, for 72 infants was CCAM ($n = 37$), sequestration ($n = 14$), hybrid association of CCAM and sequestration ($n = 10$), congenital lobar emphysema ($n = 5$), bronchial cyst ($n = 4$), or bronchial atresia ($n = 2$). No malignancy was observed in this series. Mean age at last evaluation was 2.1 ± 0.4 years.

Prenatal and Neonatal Data

The prenatal and neonatal data are presented in Table 1. Cysts were identified in 60 (71%) fetuses, and the lesion had a hyperechoic appearance in 10 of these fetuses. Signs of prenatal compression, such as mediastinal deviation ($n = 28$), ascites ($n = 3$), and polyhydramnios ($n = 7$) were observed in 29 fetuses. Delivery was preterm, before 37 weeks of gestation, in 8 cases. Nineteen infants (22%) presented with respiratory symptoms after birth (Fig 1). Five of these infants were born prematurely, and 12 required respiratory support in the form of oxygen therapy alone ($n = 1$), continuous positive airway pressure alone ($n = 4$), or tracheal ventilation ($n = 7$). Six children (7%) underwent surgery during the first 28 days of life. Two children died. An associated malformation was diagnosed in 13 infants (15%).

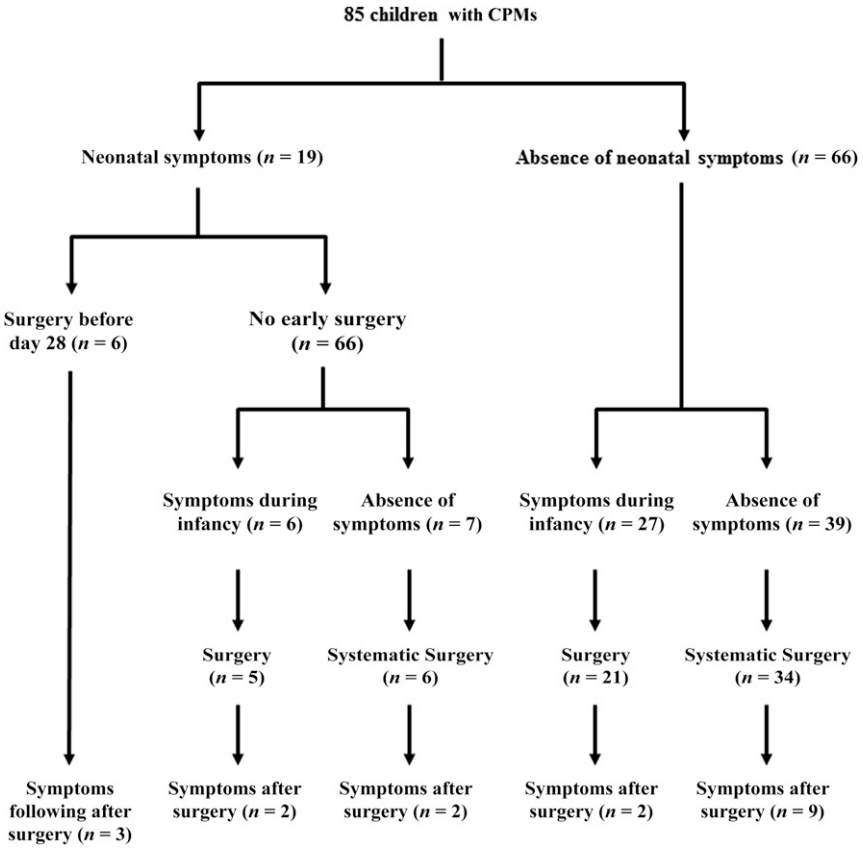

FIGURE 1
Flowchart of the study. Different periods of evaluation are considered. The neonatal period extends from birth to day 28; all symptoms and surgical excisions occurring during this period were recorded. After the neonatal period, respiratory or general symptoms were recorded from day 28 until the end of follow-up for children not undergoing surgery and from day 28 to the date of the operation for children undergoing surgery. Finally, we evaluated the occurrence of symptoms from the date of the operation until the end of follow-up for children undergoing surgery.

TABLE 2 Clinical Symptoms and Hospitalizations

Variable	Period With Conservative Management of the Malformation	Whole Period, From Day 28 to the End of Follow-up
Age at the end of the period, mo	14.7 ± 8.8	25.4 ± 5.8
Any symptom	33/79 (42)	47/83 (57)
At least 1 wheezing episode	24/79 (30)	33/83 (40)
Repeated episodes of wheezing	9/79 (11)	19/83 (23
Recurrent cough	8/79 (10)	17/83 (20
Pneumonia in the malformed lobe	1/79 (1)	1/79 (1)
Pneumonia in a nonmalformed lobe	1/79 (1)	7/83 (8)
Eating disorders	4/79 (5)	4/83 (5)
Growth impairment	6/79 (8)	6/83 (7)
Hospitalization (all causes)	10/79 (13)	11/83 (13)
Hospitalization (respiratory causes)	6/79 (8)	7/83 (8)

Data are presented as mean ± SD or observed number/total number (%). An initial analysis was performed for the period of conservative management, extending from the 28th day of life to the date of surgery, or to the end of follow-up in the absence of surgery. Neonatal symptoms, occurring before day 28, were not considered, and the 6 children who underwent surgical removal of the malformation during the neonatal period were excluded from this analysis. A second analysis was performed over the entire follow-up period, extending beyond the neonatal period, independently of surgery. All surviving children were considered in this analysis.

Postnatal Imaging

Eighty-four children underwent thoracic imaging at a mean age of 3.2 ± 4.6 months. Computed tomography (CT) scans were obtained for 83 (98%) of these children, and thoracic MRI was conducted in 1 child (1%). Imaging results were abnormal in 83 infants (99%) and showed complete regression of the malformation in 1 child. The abnormal features observed were cystic lesions (n = 54), condensations (n = 40), hyperlucent areas with or without distension (n = 21), and mucoceles (n = 2). There was a significant correlation between certain aspects of the prenatal and postnatal phenotypes, but the match was not perfect. For the 60 prenatal lesions considered cystic in appearance, 51 (85%) were considered cystic on postnatal CT imaging, whereas the other 9 presented with hyperlucent areas and/or condensations, with no evidence of cysts, on postnatal imaging. Seven of these children underwent surgery. Pathologic analysis of the lesions excised resulted in diagnoses of congenital lobar emphysema (n = 3), a hybrid association of CCAM and sequestration (n = 2), sequestration (n = 1), and CCAM (n = 1). There were 25 purely hyperechoic prenatal lesions: 20 (80%) did not appear to be cystic on postnatal CT imaging, whereas the other 5 were cystic. Four of these children underwent surgery. Pathologic criteria for the diagnosis of CCAM were present in all these patients. Associated criteria for sequestration were present in 1 case. Potentially systemic vascularization was observed postnatally in 26 children and had not been identified prenatally in 11 of these infants.

Clinical Symptoms During Infancy, Before Surgery

Among the 79 children who did not undergo surgery during the neonatal period, only 1 infant had documented infection of the cystic lobe (Table 2). Pneumonia occurred in another patient, at a site other than the malformed lobe. Eating disorders and/or poor weight gain were observed in 7 infants. Wheezing was the dominant symptom, with 30% of children presenting with ≥1 wheezing episode. Overall, 33 children (42%) had respiratory symptoms during infancy, before any surgery. Postnatal symptoms were not associated with prenatal markers of pulmonary compression, such as mediastinal compression, ascites, or polyhydramnios (Table 3). The appearance of the malformation differed significantly between infants with and without symptoms. Symptoms were more likely to occur in infancy in children with malformations that appeared noncystic prenatally (95% confidence interval [CI], 0.05–0.46; P = .01) or postnatally (95% CI, 0.04–0.47; P < .03) and in those whose lesions had a hyperlucent appearance on postnatal imaging (95% CI, 0.07–0.47; P < .01). Malformations on the left side were also more frequently associated with the occurrence of symptoms (95% CI, 0.06–0.50; P < .02).

Surgery and Changes in Symptoms

Sixty-six (84%) of the 79 children who did not undergo surgery during the neonatal period subsequently underwent surgical removal of the malformation during infancy, at a mean age of 12.4 ± 7.6 months (Fig 1). The type of surgery was thoracotomy in 24 infants, thoracoscopy in 26, and thoracoscopy converted into thoracotomy in 16. The decision to operate to excise the malformation and the timing of surgery were independent of the occurrence of symptoms beyond the neonatal period (Fig 2). Both children with pneumonia underwent surgery. The only factor found to be associated with a lower rate of surgical removal was the hyperlucent appearance of the malformation (Supplemental Table 4): 90% of children with nonhyperlucent lesions underwent surgery versus 70% of those with hyperlucent lesions (95% CI, 0.01–0.55; P < .04). Few complications occurred during the

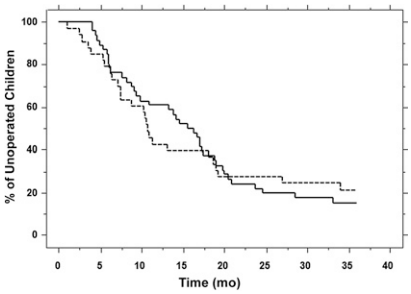

FIGURE 2
Kaplan-Meier analysis to estimate freedom from surgery, as a function of symptom occurrence. The analysis was performed for the period of conservative management, extending from day 28 of life to the date of surgery or to the end of follow-up in the absence of surgery. Neonatal symptoms, occurring before day 28, were not considered, and the 6 children who underwent surgical removal of the malformation during the neonatal period were excluded from this analysis. The solid line indicates the absence of symptoms; the dashed line indicates the occurrence of symptoms.

TABLE 3 Risk Factors for Clinical Symptoms Within the Period of Conservative Management of the Malformation

Variable	Children With Symptoms (n = 33)	Children Without Symptoms (n = 46)	P
Cystic appearance on prenatal ultrasound	18/33 (54)	36/44 (82)	.010
Right-sided malformation	13/33 (39)	31/46 (67)	.013
Prenatal systemic vascular supply	9/32 (28)	7/41 (17)	.257
Prenatal mediastinal shift	10/32 (31)	11/41 (27)	.679
Prenatal polyhydramnios and/or ascites	4/3212	3/417	.456
Gestational age at birth, wk	38.9 ± 1.6	39.2 ± 1.7	.450
Birth weight, g	3224 ± 480	3314 ± 527	.441
Respiratory symptoms at birth	6/3318	7/4615	.726
Associated malformations	7/3321	5/4511	.222
Cystic appearance on postnatal CT scan	15/31 (48)	34/46 (74)	.022
Hyperlucent appearance on postnatal CT scan	13/31 (42)	7/4615	.009
Vascular supply on postnatal CT scan	12/31 (39)	14/46 (30)	.451
Surgical removal	26/33 (79)	40/46 (87)	—
Age at surgery, mo	10.8 ± 7.8 (n = 33)	13.4 ± 7.4 (n = 46)	.736

Data are presented as observed cases/total cases, or as mean ± SD. Neonatal symptoms, before day 28, were not considered, and the 6 children whose malformations were removed by surgery during the neonatal period were excluded.

surgery or within 7 days after the surgery (Supplemental Table 5): infection, intraoperative bleeding, and pneumothorax were observed in 6%, 4%, and 10% of children, respectively. From the time of surgery to the end of follow-up, 14 (54%) of the 26 previously symptomatic children continued to display symptoms, whereas 11 (27%) of the 40 previously asymptomatic children became symptomatic. Surgery did not modify the prevalence of symptoms: 40% of the children undergoing surgery displayed symptoms after the intervention, during infancy, and 42% of children managed conservatively displayed symptoms during the period of conservative management. Six children had documented pneumonia during the postoperative period. The location of the infection was known for 4 of these patients and was on the same side as the lesion removed by surgery in 3 cases. Five of the 7 infants with general symptoms underwent surgery, leading to the complete resolution of these symptoms.

Overall, 47 of the surviving children (57%) presented with ≥1 symptom during the entire period of follow-up beyond the neonatal period, including 33 (40%) children with at least 1 episode of wheezing (Table 2). Symptoms were usually mild, with only 10 children (9%) admitted to the hospital for respiratory problems. The risk factors associated with the occurrence of symptoms over the entire follow-up period were similar to those associated with the occurrence of symptoms during the conservative management period: noncystic appearance of the malformation on postnatal imaging (95% CI, 0.01–0.43; P = .03), hyperlucent appearance of the malformation on postnatal imaging (P < .05), and malformation on the left side (95% CI, 0.08–0.51; P < .01) (Supplemental Table 6).

At the end of follow-up, 11 children were receiving inhaled corticosteroid treatment. Mean weight was 0.12 ± 1.05 SD score, and mean height was 0.68 ± 1.01 SD score. Skeletal deformities were observed in 12 children (14%): pectus excavatum (n = 10), scoliosis (n = 1), rib fusion (n = 1), and hemithoracic hypoplasia (n = 1). All the children with pectus excavatum at the end of the follow-up period had undergone surgery. In 3 patients, this deformity was first noted in the neonatal period. Surgical intervention using first-line thoracotomy, or with thoracoscopy converted into thoracotomy, was significantly associated with pectus excavatum (P < .02). This condition was observed in none of the children who did not undergo surgery, 4% of those undergoing thoracoscopy, 19% of those undergoing thoracoscopy converted into thoracotomy, and 23% of those undergoing first-line thoracotomy. Undergoing surgery early in infancy was also significantly associated with the presence of pectus excavatum at 2 years: 70% of the children with pectus excavatum underwent surgery before the age of 6 months versus only 18% of those without this condition (P < .002).

DISCUSSION

The present study is original in its prospective and multicenter nature, as well as in its inclusion of all clinical events. In previous studies, the symptom frequency was mostly estimated from limited monocentric and retrospective data. Moreover, almost all these studies focused exclusively on clinical events leading to surgery, rather than milder symptoms. Furthermore, in line with

recent recommendations,[10,11] the French database includes a standardized description of the phenotype of the CPM, preventing errors relating to the delivery of a presumed histologic diagnosis, which often proves to be false. Indeed, we found discrepancies between the results of prenatal and postnatal imaging. In 15% of children with malformations that appeared cystic on prenatal imaging, no cyst was observed on postnatal CT scans, and a minority of these children met the pathologic criteria for CCAM. Similarly, 20% of children with lesions that appeared to be purely hyperechoic on prenatal scans were found to have cysts on postnatal CT. All the children in this category who underwent surgery met the pathologic criteria for CCAM. An analysis based on phenotypic appearance thus prevented misclassification errors. Our study has some limitations. Although the French RespiRare database allowed prospective collection of data, this information is obtained via voluntary reporting, and we have no method of evaluating the completeness of reports. Furthermore, the heterogeneity of surgical strategies among participating centers might have influenced any postoperative outcome. Nevertheless, we verified that surgery did not influence the rate of symptoms.

Our results confirm a low prevalence of infection in infants with CPMs, before surgery, which was close to the value of 3% reported by Ng et al,[5] for children from the neonatal period up to the age of 5 years. Another 6 children presented documented pneumonia during postsurgical follow-up, suggesting that the lung is more susceptible to infection after surgery. It has been suggested that lobectomy affects both the ventilation and the perfusion of the resected side.[12,13] Furthermore, CPM on the left side has been identified as a risk factor for alterations on ventilation scintigraphy,[12] consistent with our results showing a significant positive association between CPM on the left side and symptoms. The presence of a malformation on the left side may therefore increase susceptibility to infection. We also observed general symptoms, such as growth impairment or eating disorders, in a minority of infants. Failure to thrive has been reported in up to 24% of children with CPM. CPM appeared to be responsible for these symptoms in all our cases because they resolved after surgery. Finally, pectus excavatum was observed in 10 of the children in our series, mostly after early surgery or surgery based on thoracotomy. The advantage of thoracoscopy in preventing these skeletal deformities has already been suggested in previous series.[14,15] Early surgery is itself a risk factor for pectus excavatum.

Our results therefore suggest that CPM is associated with a higher risk of wheezing. Prevalence values in our cohort are higher than published values for previous French prospective cohorts. Two large birth cohorts in France have provided informative data concerning the prevalence of wheezing among young children. The PARIS (Pollution and Asthma Risk: An Infant Study) birth cohort enrolled 3840 French term healthy newborn infants between February 2003 and June 2006. An evaluation of this cohort at 18 months showed occasional wheezing in 25% of infants and recurrent wheezing in 3% of infants.[16] The EDEN mother–child cohort study (Etude des déterminants pré et post natals du développement et de la santé des enfants) enrolled 2002 pregnant women at 2 French study centers. The overall prevalence of wheezing in children during the first 12 months of the survey was 22%, and the prevalence of physician-diagnosed asthma with wheezing was 7%.[17] By 2 years of age, 33% of a representative subgroup of children had experienced wheezing.[18] Some previous series suggested a fairly high prevalence of wheezing or asthma in children with CPMs. In a limited series of 21 children undergoing surgery, 19% were found to have asthma at a mean age of 7 years.[12] Infrequent episodic asthma was reported in 17% of children in another series of twelve 5-year-old children with no symptoms at birth.[19] In a recent series of children undergoing surgery, recurrent wheezing episodes were reported in 40% of the children at 7 years of age.[6] It is possible that these symptoms were not reported in most series because they were only mild and were not believed to be related to the CPMs. Indeed, only 8% of the children in our series were hospitalized for respiratory conditions. CPM-associated wheezing did not seem to be related to compression of the bronchi by the malformation. Surgery did not decrease the prevalence of symptoms; furthermore, symptoms were not associated with prenatal markers of pulmonary compression, such as mediastinal compression, ascites, or polyhydramnios.

CPMs are developmental abnormalities that occur during the pseudoglandular phase of lung development corresponding to airway morphogenesis.[20] In addition to its structural consequences, such as branching abnormalities and CPM, the disruption of lung development during this phase may also be associated with diffuse hyperresponsiveness of the airways. Transcription factor expression at the pseudoglandular stage of lung development has been shown to have a significant effect on postnatal airway responsiveness and asthma.[21] It has also been shown that Wnt signaling genes, which are differentially expressed during airway development in utero, are involved in the pathogenesis of impaired lung function in childhood asthma.[22] It is therefore tempting

to assume that the CPM is the visible part of more diffuse airway abnormalities. Consistent with this hypothesis, airway resistance, which reflects the properties of the entire airway tree, has been shown to be higher in young infants with CPM than in control subjects.[23] In older patients, prolonged expiratory flow rates were observed in most patients.[13] Another finding consistent with this hypothesis is the correlation between symptoms and a hyperlucent appearance of the CPMs reported here, providing evidence for an airway disease associated with air trapping. The fact that the CPMs with hyperlucent appearance are also those which are more frequently conservatively managed is not enough to explain this link because surgery did not change the rate of occurrence of symptoms.

CONCLUSIONS

Our findings suggest a new vision of the natural history of CPMs. Wheezing is frequently associated with CPMs, potentially induced by the pathophysiological mechanisms underlying the CPM. Surgical removal of the CPM had no significant impact on these symptoms. By contrast, surgery had several negative effects in our study, such as a paradoxical increase in pulmonary infections and the appearance of pectus excavatum after thoracotomy. Our results therefore support a conservative management for noncystic malformations. If the decision is made to perform elective surgery, our results then suggest that the operation should be performed after 6 months of age and by using thoracoscopy.

ABBREVIATIONS

CCAM: congenital cystic adenomatoid malformations
CI: confidence interval
CPM: congenital pulmonary malformations
CT: computed tomography

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