



In prenatally diagnosed CPAM, does the affected lobe influence the timing of symptom onset?

R. Sueyoshi¹ · S. Shibuya¹ · T. Ochi¹ · M. Okawada¹ · G. Miyano¹ · H. Koga¹ · G. J. Lane¹ · A. Yamataka¹

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Abstract

Purpose We investigated the relationship between the affected lobe and symptom onset in prenatally diagnosed congenital pulmonary airway malformation (CPAM).

Methods 53 CPAM patients diagnosed prenatally were reviewed retrospectively by creating 2 groups according to symptom onset. Group Sneo: (symptomatic during the neonatal period; $n=13$) and group S>neo: (symptomatic after the neonatal period; $n=40$) were compared for type of CPAM, affected lobes, types of symptoms/infections, treatment, duration of follow-up, and histopathology. Requirement for surgery (Sx) was then used to create three subgroups: Sneo + Sx, S>neo + Sx, and Sx–.

Results Some cases had multiple affected lobes. In Sneo, symptoms developed in 55.6%, 50.0%, 0%, 0%, and 36.8% of right upper lobes (RUL), right middle lobes (RML), right lower lobes (RLL), left upper lobes (LUL), and left lower lobes (LLL) diagnosed with CPAM, prenatally. In S>neo, symptoms developed in 0%, 0%, 6.3%, 55.6%, and 33.3% of RUL, RML, RLL, LUL, and LLL diagnosed with CPAM, prenatally.

Conclusion In prenatally diagnosed CPAM, RUL and RML lesions are more likely to become symptomatic in neonates, and LUL lesions in infants. Surgery is recommended before the onset of respiratory infections after 1 year of age.

Keywords CPAM · Neonatal lung infection · Symptomatic lung lesion · Pulmonary lobe morbidity · Prenatal diagnosis · Natural history pediatric lung disease

Introduction

Advances in ultrasonography (US) have enabled more morbidity to be identified on routine prenatal US, and congenital pulmonary airway malformation (CPAM) is being diagnosed with increasing frequency, posing a dilemma to neonatologists and pediatric surgeons. In cases symptomatic at birth or shortly after, surgery is generally advocated. However, there is an ongoing debate on the management of prenatally detected asymptomatic lesions. The natural history of untreated asymptomatic CPAM is essentially unknown, with only a few reports in the literature about prenatally diagnosed asymptomatic CPAM [1, 2].

To the best of our knowledge, there are no reports about the natural history of prenatally diagnosed CPAM based on location of pathology. The aim of this study was to investigate the relationship between an affected lobe and symptom onset and discuss indications for surgery.

Materials and methods

We retrospectively reviewed 53 CPAM patients diagnosed prenatally between 2002 and 2018 by creating 2 groups based on the timing of symptom development. Group Sneo ($n=13$ patients) developed symptoms during the neonatal period (up to 1 month) and group S>neo ($n=40$) developed symptoms after the neonatal period, in other words after the first month of life. We defined “symptomatic” as onset of dyspnea, and retraction on inspiration in the absence of typical symptoms of the common cold, substantiated by abnormal chest X-ray findings such as mediastinal shift.

✉ R. Sueyoshi
rsueyo@juntendo.ac.jp

¹ Department of Pediatric General and Urogenital Surgery, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, 113-8421 Tokyo, Japan

We also investigated the incidence of surgery (Sx) and outcome by creating three groups: cases symptomatic during the neonatal period who had surgery (group Sneo + Sx; $n = 13/13$), cases symptomatic after the neonatal period who had surgery (group S > neo + Sx; $n = 35/40$), and those who were observed without having Sx (group Sx–; $n = 5/40$). The surgical indication for surgery was treatment of complications of CPAM such as signs/symptoms typical of pneumonia or abscess formation (i.e., fever, raised white cell count, and raised CRP) causing distress or failure to thrive and in cases without complications, parental request. Figure 1 shows a flow chart of our study. Groups were compared for type of CPAM, affected lobes, types of symptoms/infections, treatment, duration of follow-up, and histopathology.

Statistical analysis was performed using GraphPad Prism version 6 (GraphPad Software, San Diego, CA). Bivariate analysis was performed using the Mann–Whitney U (Wilcoxon rank-sum) test for continuous variables with nonparametric distribution. For multiple group comparisons, one-way ANOVA was performed with a post hoc Tukey multiple comparison analysis. For analysis of the relationship between onset of symptoms and the affected lobe, the Fisher exact test was used. A p value of 0.05 or less was considered statistically significant. This study was approved by our institutional review board and complies with the Helsinki Declaration of 1975 (revised 1983).

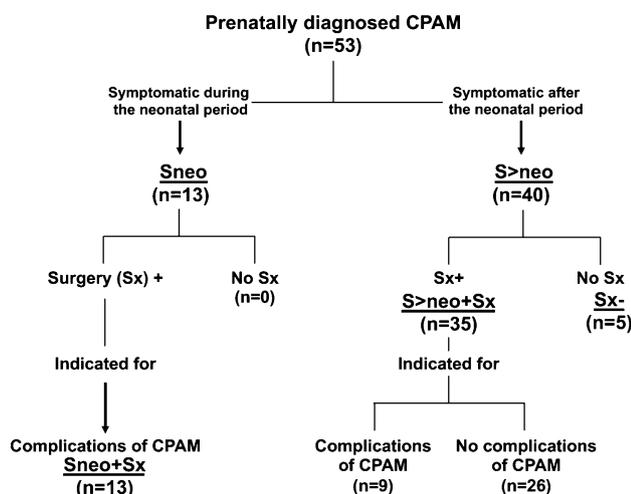


Fig. 1 Flow chart of our study. We retrospectively reviewed 53 CPAM patients diagnosed prenatally by creating 2 groups based on when patients became symptomatic; group Sneo if symptom onset was during the neonatal period and group S > neo if symptom onset was later. We also investigated the incidence of surgery and outcome by creating 3 groups; cases symptomatic who had surgery (group Sneo + Sx), cases symptomatic after the neonatal period who had surgery (group S > neo + Sx) for surgical or non-surgical indications, and those who were observed without having surgery (group Sx–)

Results

Six cases had multiple lobes affected by CPAM, so we assessed 59 lobes in 53 cases. Overall, differences in types of CPAM, affected lobes, types of symptoms/infections, treatment, and histopathology were not statistically significant.

In Sneo, 55.6% of right upper lobes (RUL), i.e., 5/9 lobes (4 with respiratory symptoms and 1 with mediastinal shift alone), 50.0% of right middle lobes (RML), i.e., 3/6 lobes (all with respiratory symptoms), 0% of right lower lobes (RLL), 0% of left upper lobes (LUL), and 36.8% of left lower lobes (LLL), i.e., 7/19 lobes (6 with respiratory symptoms and 1 with mediastinal shift alone) diagnosed prenatally with CPAM, became symptomatic (Table 1). In other words, RUL and RML lesions were significantly more symptomatic during the neonatal period ($p < .01$, respectively; Table 2).

In S > neo, 0% of RUL, 0% of RML, 6.3% of RLL, i.e., 1/16 lobes (pneumonia that commenced at 16.8 months), 55.6% of LUL (5/9 lobes, i.e., 2 with pneumonia, 2 with failure to thrive/growth retardation, and 1 with respiratory symptoms that commenced at a mean of 14.3 ± 8.9 months), and 33.3% of LLL (4/12 lobes, i.e., 3 with pneumonia and 1 with respiratory symptoms that commenced at a mean of 20.4 ± 10.1 months) diagnosed prenatally with CPAM, became symptomatic (Table 2). Onset of symptoms was significantly greater in LUL after the neonatal period ($p < 0.05$). The incidence of respiratory infections in S > neo was 6.3% in RLL (1 of 16 lobes), 22.2% in LUL (2 of 9 lobes), and 25% in LLL (3 of 12 lobes), respectively. Incidences of respiratory infections were similar in LUL and LLL.

Overall, S > neo cases were followed-up for a mean of 29.4 months (range 2–133), which averaged, 23.0 ± 15.9 months for RUL lesions, 38.9 ± 14.4 months for RML lesions, 32.4 ± 37.8 months for RLL lesions, 25.8 ± 27.0 months for LUL lesions, and 27.4 ± 15.1 months for LLL lesions. Differences in duration of follow-up according to affected lobe were not statistically significant, see Table 1. Sx– cases were observed for a mean of 77.0 ± 49.1 months (range 24–133 months). Differences in duration of follow-up according to affected lobe were also not statistically significant.

CPAM lesions had larger cysts in Sneo compared with S > neo; (30.3 ± 14.7 versus 19.0 ± 12.4 mm), but the difference was not statistically significant ($p = 0.09$), see Fig. 2a. Cysts in RUL CPAM lesions were significantly larger in Sneo than in S > neo; 37.0 ± 7.7 versus 18.3 ± 8.6 mm ($p < 0.05$). Otherwise, cysts in RML lesions were 32.3 ± 2.5 mm in Sneo and 32.5 ± 3.5 mm in S > neo. Differences between groups for RML lesion size were not statistically significant, see Fig. 2b.

Table 1 Summary of data according to affected lobes

Affected lobes ^a (<i>n</i> = 53; 59 lobes)	Follow-up (months)	Symptoms	Surgery neonatal; older	Infection neonatal; older
RUL [9]	23.0 ± 15.9	Respiratory symptoms 4 Mediastinal shift 1	5 5; 0	0 0; 0
RML [6]	38.9 ± 14.4	Respiratory symptoms 3	3 3; 0	0 0; 0
RLL [16]	32.4 ± 37.8	Pneumonia 1	1 0; 1	1 0; 1
LUL [9]	25.8 ± 27.0	Pneumonia 2 Growth retardation 2 Respiratory symptoms 1	5 0; 5	2 0; 2
LLL [19]	27.4 ± 15.1	Respiratory symptoms 7 Pneumonia 3 Mediastinal shift 1	11 7; 4	3 0; 3

RUL right upper lobe, RML right middle lobe, RLL right lower lobe, LUL left upper lobe, LLL Left lower lobe, [] Number of lobes; multiple in six cases

^aMultiple in 6 cases

Table 2 Comparison of surgery and infections according to affected lobes. Group Sneo versus group S > neo

Affected lobes ^a (<i>n</i> = 53, 59 lobes)	Incidence of surgery Group Sneo	Incidence of surgery Group S > neo	Incidence of infection Group S > neo
RUL [9]	5/9 = 55.6% <i>p</i> < .01	0% NS	0% NS
RML [6]	3/6 = 50.0% <i>p</i> < .01	0% NS	0% NS
RLL [16]	0% NS	1/16 = 6.3% NS	1/16 = 6.3% NS
LUL [9]	0% NS	5/9 = 55.6% <i>p</i> < .05	2/9 = 22.2% NS
LLL [19]	7/19 = 36.8% NS	4/12 = 33.3% NS	3/12 = 25.0% NS

RUL right upper lobe, RML right middle lobe, RLL right lower lobe, LUL left upper lobe, LLL Left lower lobe, [] Number of lobes; multiple in six cases, NS not significant

^aMultiple in 6 cases

Discussion

To the best of our knowledge, there are no reports about the natural history of CPAM based on which lobes are affected. In our series, we confirmed that CPAM diagnosed in RUL and RML prenatally became symptomatic with respiratory symptoms or mediastinal shift, significantly more frequently during the neonatal period at rates of 55.6% and 50%, respectively. Laje et al. demonstrated that large CPAM lesions can also induce respiratory distress after birth due to pulmonary hypoplasia caused by mass effect [3].

Surprisingly, while RUL and RML affected by CPAM were significantly more symptomatic during the neonatal period, none became symptomatic after the neonatal

period. Thus, when RUL or RML lesions are diagnosed prenatally, parents should be counselled to expect their child to become symptomatic early, with a high possibility of early surgical intervention before there is too much damage to the lungs, especially if lesions are large.

Similarly, LUL was the only lobe that was significantly more symptomatic (55.6%, 5/9 lobes) after the neonatal period. Of pneumonia, failure to thrive, and respiratory symptoms associated with CPAM in LUL, only failure to thrive/growth retardation was exclusive to affected LUL. Just as chronic lung disease (CLD) causes increased energy expenditure because of labored breathing, neonates/infants with CLD will manifest failure to thrive/growth retardation as well [4]. When we assessed the clinical courses of the two cases in this series with failure to thrive/growth retardation, the physiological influence of CLD was plausible, but in

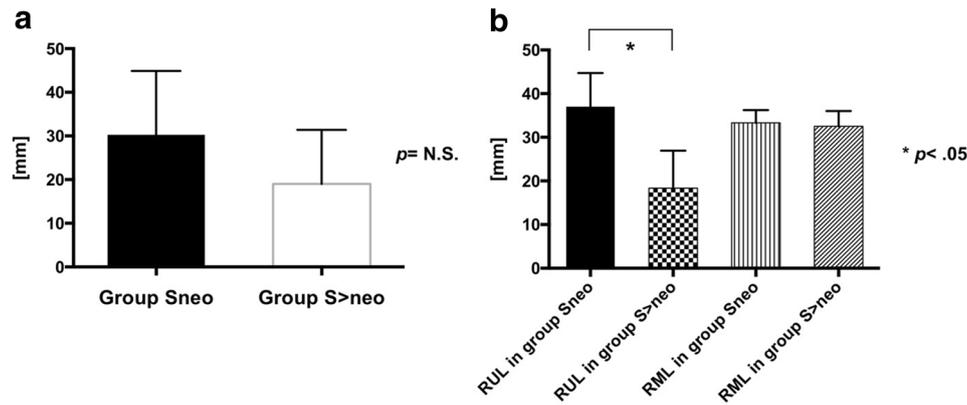


Fig. 2 a Cyst size of CPAM lesions (group Sneo versus group S>neo). Cysts were larger in group Sneo than in group S>neo (30.3 ± 14.7 versus 19.0 ± 12.4 mm), but the difference was not statistically significant. Analysis was performed using the Mann-Whitney U test with nonparametric distribution. **b** Cyst size of CPAM lesions

in RUL and RML (group Sneo versus group S>neo). Cysts in RUL lesions were significantly larger in group Sneo than in group S>neo; 37.0 ± 7.7 versus 18.3 ± 8.6 mm ($p < 0.05$). Analysis was performed using the one-way ANOVA with a post hoc Tukey multiple comparison analysis

addition, we began to wonder whether the left superior lobe bronchus being more cranial than the right superior lobe bronchus may influence ventilation of the LUL. We plan to investigate the ventilation volume of the LUL preoperatively using lung ventilation scintigraphy in the future.

Although it has been reported that one-third of respiratory infections associated with CPAM occur in the first year of life [5], we did not experience any respiratory infections until after 12 months of age; in fact, the mean onset of respiratory infections in this study was 20.3 months (range 12.4–35.2 months) and the overall incidence in all lobes in our study was 9.4% (5 of 53 cases) which is similar to other reports in the literature [6, 7], even though the incidences of respiratory infections in LUL and LLL were 22.2% and 25.0%, respectively. Because the mean onset of respiratory infections was 20.3 months, with the longest case taking some 35 months to develop a respiratory infection, our mean follow-up of 29.4 months is more than long enough to cover the period during which respiratory infections are most likely to occur, which we believe gives us further insight into the natural history of prenatally diagnosed CPAM.

Nevertheless, the management of asymptomatic prenatally diagnosed CPAM is controversial. Reports in the literature indicate that there is trend away from open lobectomy to thoracoscopic lobectomy [8]. While minimally invasive surgery has numerous advantages, thoracoscopic lobectomy is greatly complicated by pathology and anatomic anomalies associated with CPAM and adhesions [9]. In particular, LUL lobectomy is prone to anomalous vasculature and from experience can be difficult.

Cook et al. reported that surgery for recurrent respiratory infections is most frequently performed in 1 year with a decrease after 2 years [2]. In a previous study, we found that the incidence of intra/postoperative complications in a group

of CPAM patients was unrelated to a past history of abscess formation [10], suggesting that past histories of pneumonia or abscess formation should not be considered as contraindications to thoracoscopic surgery in CPAM patients, but that operative time will be longer for thoracoscopic surgery in such cases because of severe adhesions.

In summary, the onset of symptoms in prenatally diagnosed CPAM differs according to the affected lobe, with RUL or RML lesions becoming symptomatic during the neonatal period, and LUL lesions becoming symptomatic after the neonatal period. We found that the natural history of prenatally diagnosed CPAM was for respiratory infections to manifest after 12 months of age, with a peak at 20.3 months, and consequently, surgery should be planned accordingly. In other words, CPAM patients with RUL or RML lesions should be actively considered for early surgery (during the neonatal period) and observed closely with this in mind, especially if cystic lesions in the RUL or RML are large, and CPAM patients with LUL or LLL lesions would benefit most from surgery before the risk for respiratory infection increases after 1 year of age to facilitate surgery and minimize growth retardation.

Compliance with ethical standards

Conflict of interest The authors declare that there were no conflicts of interest.

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