**MORBIDITY AFTER ELECTIVE RESECTION OF PRENATALLY DIAGNOSED ASYMPTOMATIC CONGENITAL PULMONARY AIRWAY MALFORMATIONS**

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**ABSTRACT**

**Background/Aim:** The optimal management of prenatally diagnosed asymptomatic congenital pulmonary airway malformations (CPAM) is controversial. Since there is a paucity of data relating to surgical risks in this specific population, we reviewed our experience to further inform this controversy.

**Methods:** Ethically approved 10 year (2004-2013) retrospective review. Patients were included only if the CPAM was diagnosed prenatally and remained asymptomatic. Indication for surgery was physician recommendation and/or parental choice.

**Main results:** Sixty patients were identified. Median age at surgery was 6.5 months (range 65days-9.6years). Resections were performed thoracoscopically (n=51, 1 conversion) or by thoracotomy (n=9). Surgical time was 2.5 hours (43minutes–4.75hours). A chest drain was used in 57/60 and remained in situ 53 hours (23-108). There were no intra-operative complications or blood transfusions. All patients were extubated at the end of the procedure with no re-intubations. Post-operative hospitalisation was 73.4 hours (23.8hrs-4.2days) hours. Overall, complications occurred in 14/60 (23%). Eleven were minor but 3 were major: tension pneumothorax associated with new presentation of a small previously undiagnosed diaphragmatic hernia 5 days following resection; aggressive fibromatosis of the chest wall in the region close to resection 2 years later; and near-fatal hypovolemic cardiac arrest due to massive haemorrhage from a feeding vessel on postoperative day 7. There were no deaths and no cases of pleuropulmonary blastoma.

**Conclusion:** Resection of prenatally diagnosed asymptomatic CPAM is associated with a significant risk of complications, which may be life threatening. These data contribute to a balanced discussion of risks and benefits for these children.

**INTRODUCTION**

Congenital pulmonary airway malformations (CPAM) are being detected with increasing frequency 1,2, likely due to advances in prenatal imaging technology and techniques. When a CPAM is associated with symptoms, there is general agreement that excision is appropriate. However, many of these lesions decrease in size during fetal life 3,4,5 and the majority are asymptomatic at the time of birth. The optimal management strategy for this group of prenatally diagnosed and postnatally asymptomatic children is controversial 6,7. Traditionally most pediatric surgeons have recommended elective surgical excision during infancy 8,9,10 but more recently some authors have suggested that expectant observation is also a reasonable approach 11,12,13. The controversy revolves around balancing the risks of CPAM, which include infection and cancer, against the risks of surgery and possible long-term functional impairment associated with loss of pulmonary parenchyma 14,2,6,15,7,16,17. Although a number of authors have documented risks associated with pulmonary resection during childhood 9,18,19,20,21,22, there are few studies that have examined these risks specifically in the population of children with prenatally diagnosed asymptomatic CPAM. The present study was designed to document the risk of surgery for prenatally diagnosed asymptomatic CPAM in order to further inform the controversy surrounding routine surgery in this patient population.

**METHODS**

We reviewed the charts of all consecutive children (age <18yrs) who underwent surgical excision of a CPAM during the 10 year period from January 2004 to December 2013 at the Hospital for Sick Children, Toronto. For the purposes of this study, CPAM was defined as any cystic, solid, or mixed lung lesion detected on prenatal ultrasound. This term incorporates the full spectrum of lesions which have been traditionally known as congenital cystic adenomatoid malformation, bronchopulmonary sequestration, congenital lobar emphysema, or bronchial atresia. Only those in whom the lesion was diagnosed prenatally and remained asymptomatic were included in this report. Furthermore this report includes only those cases in which resection was performed. In all cases, the decision to proceed with excision was based upon a discussion between the parents and surgeon in which full disclosure of the potential risks and benefits of the two management strategies was provided. When the joint decision was to proceed with surgery, resection usually took place after 3 months of age. Demographic and clinical data were retrieved from the patient charts and operating room records with particular emphasis on surgical outcomes including but not limited to operative times and procedure performed, duration of chest drain, post-operative length of hospitalisation, peri- and post-operative complications and final pathology result (described in accordance with the most recent Stocker classification 23). Complications were classified as major if they required surgical intervention and minor if they did not, based on the widely used Clavien-Dindo classification of surgical complications.24 Data are reported as median and range. Statistical comparisons were made using Mann-Whitney U test or Fisher’s exact test as appropriate.

The initial operative approach was based on surgeon preference, and consisted of either lateral thoracotomy or thoracoscopy. Where indicated, anatomical resection (i.e. lobectomy) was performed. For thoracoscopic procedures, resection was facilitated by the use of an energy device and/or surgical clips to seal vessels whilst main bronchi or subdivisions were divided and sealed using an endoscopic stapling device, clips or sutures.

The study was approved by The Hospital for Sick Children Research Ethics Board (Ref: 1000040806).

**RESULTS**

During the study period a total of 111 children underwent resection of a CPAM at our institution. Sixty children (29 male) met the inclusion criteria (prenatal diagnosis and asymptomatic) and all were included in this review. For these 60 children, median age at surgery was 6.5 months (range 65 days - 9.6 years). The oldest child in this series had resection of an asymptomatic lesion following 9 years of expectant observation due to a change in parental attitude. Resection was performed thoracoscopically in 51 cases with 1 conversion for inadequate visualisation and by thoracotomy in 9 cases. Median overall surgical time was 2.5 hours (43 minutes - 4.7 hours) and was similar for open resection (2.9 hours [1.5 - 4.3]) and thoracoscopic resection (2.6 hours [43 minutes - 4.7 hours]).

Fifty-three children had an anatomical resection of one or more pulmonary lobes including 4 children who had resection of two lobes and 3 children who had a lobectomy combined with a non-anatomical partial resection of an adjacent lobe. The remaining 7 lesions were extralobar or non-anatomic resections for pathologies that included all pure bronchopulmonary sequestrations and some hybrid lesions (Table 1). The lower lobes were most frequently involved (46 cases) and 31 lesions were on the right side. One child had an esophageal diverticulum resected at the same time as the CPAM lesion in the right lower lobe. Final pathological diagnosis is shown in Table 1. There were no cases of pleuropulmonary blastoma.

Complications

There was 1 intra-operative complication consisting of a blocked endotracheal tube due to a blood clot. The child was re-intubated without consequence. There were no blood transfusions and all patients were extubated at the end of the procedure with no post-operative re-intubations prior to discharge. Two children had a planned overnight stay in the Intensive Care Unit for monitoring due to co-existing cardiac morbidities. A chest drain was used in 58/60 with the remaining 2 cases of extralobar sequestration without airway connection treated successfully without a chest drain. The chest drain remained in situ for a median of 53 hours (23 - 108). Median post-operative hospitalisation was 73.4 hours (23.8 hours – 11.2 days).

Post-operative complications occurred in 14/60 children (23%) and are summarised in Table 2. Eleven were classified as minor on the basis that they resulted in an additional period of hospitalisation (delayed discharge [n=9] or re-admission [n=2]) but resolved either spontaneously without additional intervention or with antibiotics alone. The remaining 3 complications were classified as major and are described below in greater detail. Initial length of hospital stay following surgery (not including any hospitalisation for re-admission) was significantly longer in children who suffered a complication than those who did not (no complication median 72.9 hours (23.8 hours – 6.5 days) *vs* complication 97.5 hours (42.3 hours – 11.2 days); p=0.004). There were no deaths in this series.

All but one of the complications occurred in children undergoing thoracoscopic as opposed to open resection. However there was no statistically significant difference in incidence of minor, major or total complications between open and thoracoscopic approaches.

Major complications

*Patient 1* underwent thoracoscopic non-anatomical resection of a right lower lobe CPAM found on pathology to be a congenital cystic adenomatoid malformation (type 2). Surgery was uneventful but the child re-presented with a large pneumothorax and evidence of bowel in the right chest on post-operative day 5. Thoracoscopic repair of what appeared to be a previously unrecognized congenital lateral diaphragmatic defect was performed. This child had several recurrent pneumothoraces requiring chest tube drainage over the following three weeks. Subsequent recovery has been satisfactory.

*Patient 2* underwent thoracoscopic resection of a right upper lobe CPAM and had an uneventful recovery. Pathology of the CPAM revealed congenital cystic adenomatoid malformation (type 2). Two years later he presented with a large non-resectable mass confirmed on biopsy to be aggressive fibromatosis arising from the right chest wall at a previous port site. The child is being treated with chemotherapy with some reduction in size of the lesion.

*Patient 3* underwent thoracoscopic left lower lobectomy for a CPAM with a large systemic feeding vessel. The feeding vessel was secured with a clip on the aortic side, and a sealing device was used on the pulmonary side. Pathology demonstrated a large intralobar bronchopulmonary sequestration. One week postoperatively he presented to the Emergency department with out-of-hospital hypovolemic cardiac arrest. Emergency department thoracotomy was required to control massive hemorrhage from the feeding vessel which was only possible after the child had been placed on ECMO. The child survived and was discharged after 30 days, with close neurological follow-up planned.

Follow-up

Duration of follow-up (time between surgery and last seen in the out-patient clinic) was median 92 days (14 days – 4.4 years). With the exception of the previously described child with aggressive fibromatosis and 1 child in whom complete resection of a type 2 CPAM was not possible due to bilobar disease, and who has normal pulmonary function tests but occasionally requires bronchodilators, no children were symptomatic at follow-up.

**DISCUSSION**

The decision of whether or not to resect a prenatally diagnosed, asymptomatic CPAM in an otherwise healthy child continues to challenge surgeons and polarises opinion amongst the pediatric surgical community. The existing literature contains multiple recommendations from many authors citing indications for surgical excision and expectant observation alike. Arguments in favour of routine resection 7,8 include the long-term risk of infection, difficulty differentiating CPAM from PPB based on radiological appearance 17, a long-term risk of cancer in congenital cystic lesions 25, and the theoretical optimization of compensatory lung growth if the lobectomy is done during infancy 14. Arguments against routine resection 6,2 include evidence that infection may only occur in a small percentage of cases 26, the recognition that both PPB and late development of cancer are extremely rare 25, a lack of evidence that early lobectomy results in better compensatory lung growth 27, and a recognizable level of risk to the operation itself 22,18. Unfortunately, the quality of the data supporting each of these rationales is relatively poor and the indications for resection in an asymptomatic child are all *relative*. Ultimately, it falls upon the surgeon to inform the family of the relative risks and benefits of each management strategy so that an informed decision can be reached.

In this study we have focused on the risks of the surgical procedure itself, since these risks are an important part of the risk/benefit discussion with the family, and because reliable data on the risks of surgical excision in this precise patient population (specifically prenatally diagnosed, asymptomatic lesions) are sparse. Whilst there are many reports of surgical excision of CPAMs, most include a combination of symptomatic and asymptomatic patients who were diagnosed both pre- and postnatally. Where outcomes for the specific patient population of interest are documented, case volume is often small. To our knowledge, the report by Tsai et al that documented the outcomes for 105 prenatally diagnosed, asymptomatic children is the only previous large clinical volume study 28.

Over the past decade, there has been increasing use of a minimally invasive approach to excision of CPAMs in children. Stanton et al’s meta-analysis of 41 series published in 2008 identified a minimally invasive approach in just 53 of 1070 (6%) symptomatic and asymptomatic lesions 26. Nasr and Bass’s meta-analysis of open *versus* thoracoscopic resection of CPAMs (also a mix of symptomatic and asymptomatic lesions) included just 56 thoracoscopic resections in 6 studies 29. More recently, Rothenberg has published his series of 97 pediatric minimally invasive lobectomies for a variety of diagnoses and indications 19. Our experience mirrors that of the published literature with an increasing adoption of a minimally invasive approach to resect these lesions. Since the beginning of 2006 all procedures in our series were commenced thoracoscopically and there has been just 1 conversion to thoracotomy since then due to inadequate visualisation to safely complete the dissection.

Our series, therefore, contributes a relatively large number of patients treated by contemporary surgical techniques to the existing evidence base. The key finding of our review is the high proportion of children who developed a complication (23%). Although the majority of these were mild and resolved with either no additional intervention or with administration of antibiotics alone, many of them resulted in additional morbidity and prolonged hospital stay. Further the one child in our series who had bilobar disease underwent incomplete resection and is left with residual radiological cystic changes and occasional need for bronchodilators. It is impossible to know whether the residual disease is the cause of these respiratory symptoms. However, the presence of bilobar cystic lung disease increases the chances of the lesion being a pleuropulmonary blastoma, and these lesions should therefore all undergo at least partial resection to rule out this possibility.25

Most importantly, our concern is focused on the 3 cases in this series that had a major complication, two of which were potentially life-threatening. These factors must form part of the discussion between surgeon and family when the appropriate management strategy is formulated.

It is impossible to be sure whether two of the major complications (Patients 1 and 2) were a direct result of resection. For Patient 1, there was a direct temporal association between resection and the development of a large pneumothorax, strongly suggesting that the pneumothorax was a result of the operation. Furthermore, it is more likely that the pneumothorax unmasked the previously unrecognized congenital diaphragmatic hernia, rather than causing it. Trauma (including surgical trauma) has been proposed in the aetiology of up to 1 in 4 cases of fibromatosis30, and the location and timing of the development of fibromatosis in Patient 2 strongly suggests an etiological link between the two entities. For Patient 3, it is unclear why the clip became dislodged 7 days after the operation. We hypothesize that the heat from the sealing device may have weakened the tissue, and we have abandoned the combined use of clips and a sealing device as a result of this case.

The overall complication rate in our series is higher than that reported by Tsai and colleagues who reported a 7% complication rate consisting mainly of air leak and need for blood transfusion 28. It is possible that the higher complication rate in our series is due to a lower threshold for reporting of complications such as fever and pleural effusion, which were not reported in the Tsai study. It is also possible that selection bias may have played a role, since we have taken a selective approach to resection and may be observing some of the smaller lesions (which may be inherently associated with a lower risk of complications) that were resected in the Tsai series. An additional difference between series is the fact that most of our cases utilized a minimally invasive approach. However, Albanese and colleagues reported a zero complication rate in a small series of 14 thoracoscopic resections for an identical patient population that we have studied 31 and Vu et al reported a trend (p=0.05) towards *lower* complication rate with thoracoscopic compared to open resection in a series of 22 asymptomatic children 20. In their meta-analysis comparing open with minimally invasive resection, Nasr and Bass identified complications following both open and thoracoscopic surgery but found no statistically difference in the incidence of complications between operative approaches 29. There was no statistically significant difference in complication rate between open and thoracoscopic approaches in our series.

Mortality after elective resection of an asymptomatic CPAM has only rarely been reported 32. This kind of complication is subject to reporting bias, since we are aware of at least three deaths which have occurred during thoracoscopic resection of an asymptomatic lesion which have not been reported. Despite its rarity, death should be included in the list of possible outcomes when discussing the risks and benefits of resecting an asymptomatic CPAM. We believe it should also be disclosed during the process of gaining informed consent for surgery.

These data demonstrate that resection of a prenatally diagnosed asymptomatic CPAM is associated with a significant risk of complications, which occasionally may be life-threatening. These data are useful in informing a balanced discussion of risks and benefits for these children and that resection of an asymptomatic CPAM should not be undertaken without due consideration of the risks. We recommend that surgeons who recommend routine resection for all prenatally diagnosed asymptomatic lesions carefully evaluate the relative risks of resection versus continued observation for this population. Finally, further multicentre prospective studies are needed to generate additional high quality data surrounding all of the risks and benefits on both sides of this controversy.

**TABLE TITLES AND LEGENDS**

**Table 1: Final pathological diagnosis of resected congenital pulmonary airway malformations**

CCAM – congenital cystic adenomatoid malformation

\*typically a mixed lesion with components of both CCAM and bronchopulmonary sequestration, including a systemic arterial supply

**Table 2: Complications according to Dindo24**

\* spontaneous resolution without antibiotics, delayed discharge for 24 hours in each case

$ defined as fever and tachypnea with clinical and radiological examination consistent with underlying pulmonary consolidation and treated with a course of antibiotics

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