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ORIGINAL ARTICLE

Subpleural lung cysts in Down syndrome: prevalence and association with coexisting diagnoses

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Abstract
Background Although subpleural cysts are known to be associated with Down syndrome, their etiology and prevalence remains unknown.
Objective To determine the prevalence of subpleural cysts in children with Down syndrome and the association with prematurity, congenital heart disease (CHD), extracorporeal membrane oxygenation (ECMO), and chronic ventilator support.
Materials and methods A review of the CT examinations of 25 children with Down syndrome was performed to determine the presence, location, and distribution of cysts along with associated abnormalities. Charts were reviewed and coexistent diagnoses and past treatments were recorded.
Results The prevalence of subpleural cysts was 36% with no significant association with CHD, ECMO, or chronic ventilator support. An association was found in the two children with a history of prematurity. The cysts were most commonly found in the anteromedial portion of the lung.
Conclusion Subpleural cysts are common in Down syndrome and should not be confused with another pathological process. An association with prematurity was found, but the low number of children in this study makes the connection uncertain. The etiology remains unclear, but it has been hypothesized that the cysts are associated with lung hypoplasia.

Keywords Down syndrome · Subpleural cysts · Lung hypoplasia · Children

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Introduction

Subpleural lung cysts are small cystic dilatations along the subpleural surface of the lungs. On histology they have been found to communicate with the subpleural alveoli [1]. The first association of these cysts with Down syndrome (trisomy 21) was reported in 1986 in two infants who were found to have cystic lung disease at autopsy [2]. They both had congenital heart disease. Few radiological studies of this association have been performed. One study was a case series examining chest radiographs from 45 children with Down syndrome. Only one child in this series had findings suggestive of subpleural cysts, and there was no CT confirmation of this finding [3]. It is difficult to detect small subpleural cysts on plain chest films, and it is possible that these past radiological studies underestimated the prevalence of these cysts in children with Down syndrome. A radiological series examining the prevalence of subpleural cysts using CT has not been reported in the medical literature. The purpose of this study was to better define the prevalence and the location of subpleural cysts in children with Down syndrome who have undergone CT imaging and to assess the cysts' associations with coexistent diagnoses.

Materials and methods

Institutional review board approval for the study was obtained from the authors' institution, The Children's Hospital of Philadelphia in Philadelphia.

This retrospective case series identified children with Down syndrome who had undergone chest CT at The Children's Hospital of Philadelphia. The radiology information system (RIS) was searched for children with a clinical history of Down syndrome, or trisomy 21, who had undergone chest CT in an 8-year period from 1999 to 2007; a total of 26 children were identified. However, because of the typical histories provided within the RIS, this number of children might have been an underestimation of the number of children with Down syndrome. Of the children identified, one not of pediatric age at the time of imaging was excluded from the study. Three children underwent multiple chest CT scans. Although all CT scans were reviewed, the most recent scan was used in the statistical analysis. To our knowledge none of the children underwent a lung biopsy, so there is no histological correlation for the imaging findings.

Image analysis

The CT examinations were performed according to the standard clinical protocol at the time of the examination, and during the 8-year period of this study, the standard clinical protocol varied greatly. All scans were performed on a multidetector CT system. All but two of the scans were performed with intravenous contrast agent. The slice thickness varied from 0.75 to 6.5 mm. The smallest slice thickness was obtained from the one child who had a CT angiogram. No high-resolution CT examinations were performed. The tube current was adjusted for child age/size using a color-coded chart, and on the most recent studies automatically modulated mAs was used. The tube voltage ranged from 90 to 120 kVp.

The CT scans were analyzed independently by two radiologists. Subpleural cysts were defined as small cystic dilatations along the subpleural surface of the lungs. The CT scans were analyzed for the presence or absence of subpleural cysts, for the location of the cysts (anterior/posterior, medial/lateral, peripheral/fissural/bronchovascular bundles), and for the presence of intraparenchymal cysts. Associated lung findings were also noted. In the event of discrepant findings, a final decision was reached by consensus. The radiologists were blinded to the children's clinical information during the review.

Clinical information review

Patient charts were subsequently reviewed, and information including gender, age at the time of CT imaging, coexistent diagnoses such as prematurity and congenital heart disease, and past treatments with either extracorporeal membrane oxygenation therapy (ECMO) or chronic ventilator support was recorded. Prematurity was defined as birth before 34 weeks' gestation. Chronic ventilator support was somewhat arbitrarily defined as ventilator dependence for longer than 1 month.

Statistical analysis

A frequency calculation was performed to determine the prevalence of subpleural cysts and the different locations of the subpleural cysts in the patient population. A chi-squared

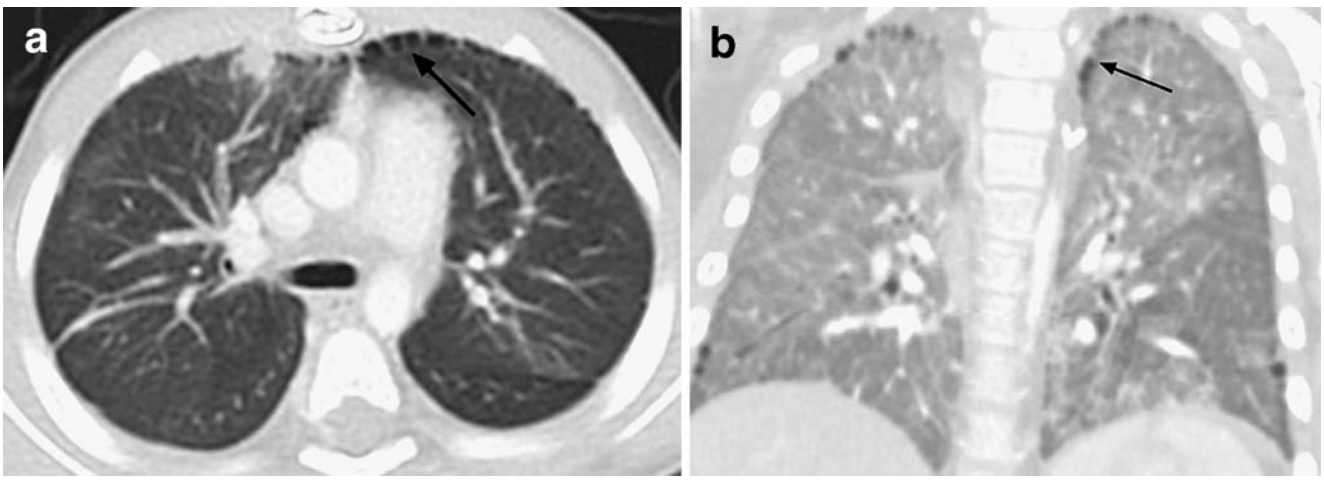

Fig. 1 Peripheral subpleural cysts (*arrows*). **a** A 3-mm axial reconstructed contrast-enhanced CT image in a 3-year-old boy. **b** A 2-mm coronal reconstructed contrast-enhanced CT image in an 8-year-old girl

test was then used to test for the association of subpleural cysts with secondary diagnoses. *P* values less than 0.05 were considered statistically significant.

Results

The 25 children identified ranged in age from 3 months to 20 years (mean±SD, 7.3±5.2 years) at the time of chest CT scan, and 13 were boys and 12 were girls. Of these 25 children, 9 (36%) had subpleural cysts. These 9 children ranged in age from 3 months to 6 years (mean±SD, 5.5±3.3 years), and 5 were girls and 4 were boys. The subpleural cysts were located in the anteromedial portion of the lung in all nine children, and were located only within the anteromedial portion of the lung in four of the nine (44%) (Fig. 1). In addition to the periphery of the lung, cysts were found along the lung fissures in four children (44%) (Fig. 2). Two of the nine children (22%) had cysts along the bronchovascular bundles in addition to the pleural surfaces (Fig. 3). One child (11%) had cysts only in the periphery of the left hemithorax with associated pleural thickening (Fig. 4). No intraparenchymal cysts were noted.

Demographic and clinical data of the nine children with subpleural cysts are presented in Table 1. Two of the children (22%) had a history of prematurity, eight (89%) had a history of congenital heart disease, and four (44%) had a history of chronic ventilator support. All children with a history of chronic ventilator support had a history of congenital heart disease. There were no children with subpleural cysts who had a history of ECMO therapy. The prevalence of subpleural cysts in relation to the children's history and coexistent diagnoses is presented in Table 2. Both children with prematurity had subpleural cysts (*P*=0.049),

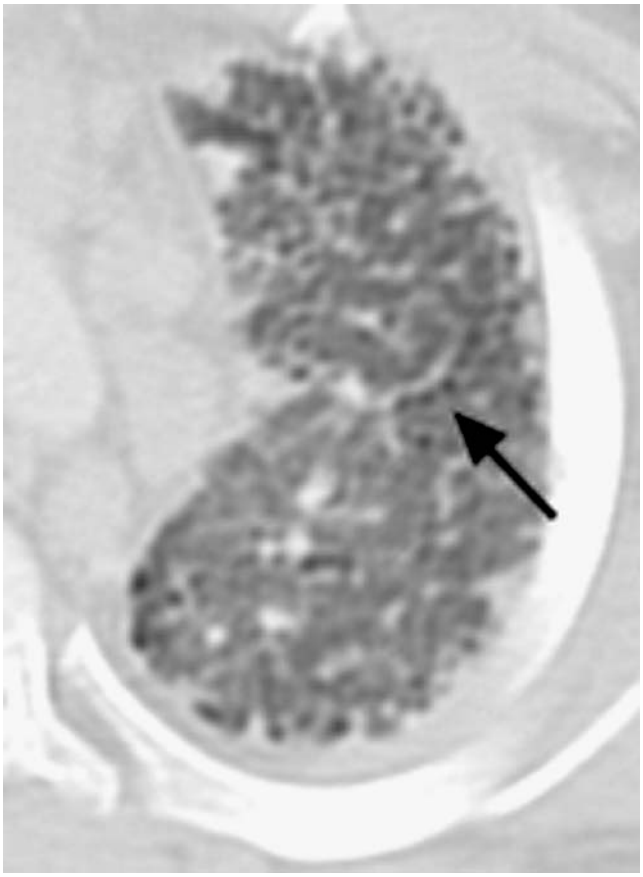

Fig. 3 Magnified view of a 5-mm axial reconstructed contrast-enhanced CT image of the chest in a 6-year-old boy demonstrates cysts extending along the bronchovascular bundles (*arrow*)

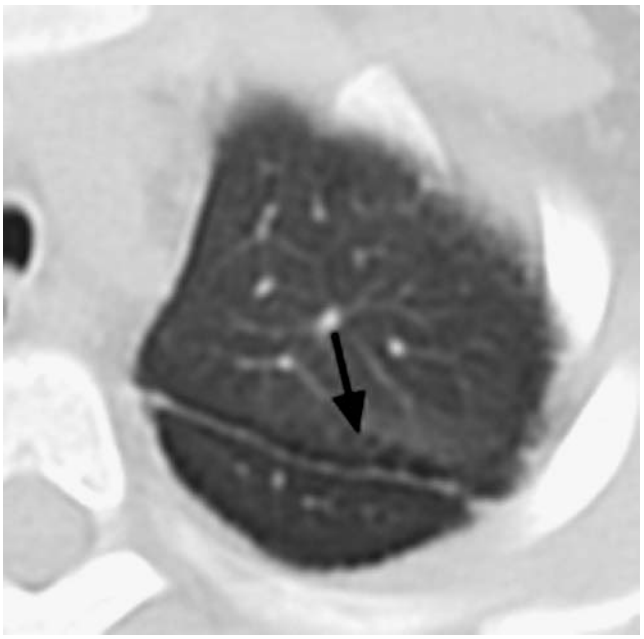

Fig. 2 Magnified view of a 5-mm axial reconstructed unenhanced CT image of the chest demonstrates subpleural cysts along the pleural reflections of the left major fissure (*arrow*)

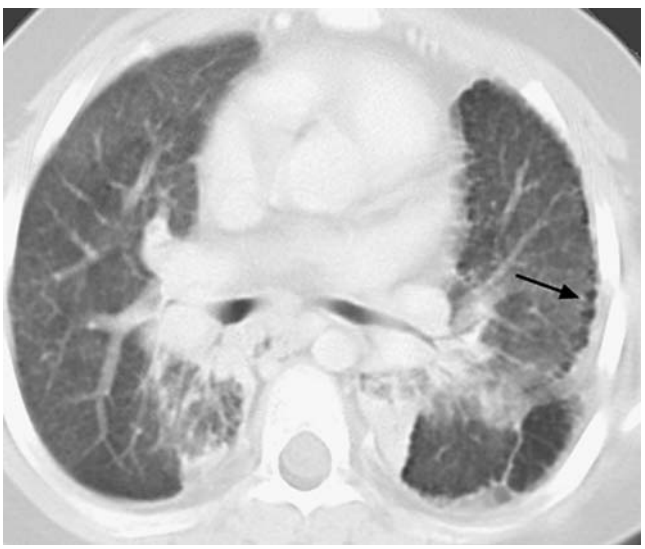

Fig. 4 A 6.5-mm axial reconstructed contrast-enhanced CT image in a 7-year-old girl shows subpleural cysts present only within the left hemithorax with pleural thickening (*arrow*)

Table 1 Demographic and clinical data of the nine children with subpleural cysts

Sex	Age	Location of cysts	Secondary diagnoses/history
M	3 months	Anteromedial bilateral only	Congenital heart disease
M	3 years	Anteromedial bilateral only	Congenital heart disease
M	8 years	Anteromedial bilateral only	None
F	10 years	Anteromedial bilateral only	Congenital heart disease, chronic ventilator support
F	17 months	Diffusely bilateral within the periphery, and along fissures	Congenital heart disease
F	6 years	Diffusely bilateral within the periphery, and along fissures	Congenital heart disease
M	6 years	Diffusely bilateral within the periphery, along fissures, and along bronchovascular bundles	Congenital heart disease, premature birth, chronic ventilator support
F	8 years	Diffusely bilateral within the periphery, along fissures, and along bronchovascular bundles	Congenital heart disease, chronic ventilator support
F	7 years	Diffuse only within the periphery of the left hemithorax	Congenital heart disease, premature birth, chronic ventilator support

which was the only statistically significant association with a secondary diagnosis. Of the 19 children with a history of congenital heart disease, eight had subpleural cysts (42%, P=0.2). Given that all children with a history of chronic ventilator support also had a history of congenital heart disease, this variable could not be analyzed independently given the small number of children. The three children with multiple scans had similar findings on all scans. None of these children was found to have subpleural cysts.

Discussion

Subpleural cysts are not unique to but are suggestive of Down syndrome. Only two children without Down syndrome were found to have subpleural cysts in a review of a pathology database of approximately 8,000 children [1]. Of the two non-Down syndrome children with subpleural cysts, one had a history of congenital heart disease. The largest case series investigating the association of subpleural cysts and Down syndrome was an autopsy series of 89 infants among whom 20% were found to have subpleural cysts [1]. We found that the prevalence of subpleural cysts detected by chest CT in children with Down syndrome at our institution was 36%. Given the limitations of our search in the RIS, some children with Down syndrome who underwent a chest CT scan might not have been identified, and therefore the prevalence in our institution could be higher.

Although the etiology of these cysts is unknown, pulmonary hypoplasia is a feature of Down syndrome and might be related to their development. Children with Down syndrome have been found to have a diminished number of alveoli, a smaller alveolar surface area, and enlarged alveoli and alveolar ducts [4]. Histologically, the cysts have been shown to be in continuity with the proximal air passages. The subpleural cysts have been noted to be approximately 0.1–0.2 cm in diameter and consist of flat and cuboid epithelial cells with intervening fibrous tissue [1].

It has been postulated that the reduced production of air spaces occurs early in postnatal life; this is supported by the absence of subpleural cysts within the stillborn infants in an autopsy series. The youngest infant with cysts in that series was 3.5 weeks old [1]. In our study, the youngest child noted to have subpleural cysts was 3 months old; this child was also the youngest child imaged.

A significant association between subpleural cysts and congenital heart disease in children with Down syndrome has been reported in past case series [1, 2]. We did not detect a significant association, which could be because of the smaller number of children in our study. Although we found that a history of prematurity was significantly associated with subpleural cysts, this result should be interpreted with caution because the number of children with a history of prematurity in the study was low.

In a small case series of two children with Down syndrome and subpleural cysts, it was hypothesized that the presence of subpleural cysts contributed to higher morbidity and mortality caused by congenital heart disease [5]. This theory was based on the observation that the age of death of children with subpleural cysts ranged from 3.5 weeks to

Table 2 Prevalence of subpleural cysts in relation to clinical history and coexistent diagnoses

	No. of children	Percentage with subpleural cysts	P value
Congenital heart disease	19	42	0.2
Premature birth	2	100	0.049
ECMO therapy	2	0	0.3

12 years, with half of the children affected being younger than 1 year [2, 5]. Our data demonstrated subpleural cysts in a child as old as 10 years.

Although the clinical relevance of subpleural cysts in Down syndrome is poorly understood, it is still important not to confuse this common finding with other pathology. Even in an institution such as ours, which is a dedicated children's hospital with fellowship-trained pediatric radiologists, this finding was misinterpreted as honeycombing in one of the children listed above. Furthermore, the subpleural cysts extending along the bronchovascular bundles should not be mistaken for intraparenchymal cystic lung diseases such as lymphangioleiomyomatosis or cystic bronchiectasis, or for peripheral fibrosis as seen in collagen vascular diseases.

Limitations of our study include the relatively low number of children and limited image resolution resulting from technique and breathing motion; however, we are not aware of any previously published radiological CT series describing these findings. A further limitation is that most of the children included in this study had significant respiratory or cardiovascular comorbid disease; the prevalence of subpleural cysts might differ in asymptomatic children with Down syndrome.

Conclusion

Subpleural cysts within the lungs are a common finding on chest CT in children with Down syndrome; such cysts are important to recognize and not confuse with other pathology. They are most commonly located within the anteromedial portion of the lung. The etiology of the cysts remains unclear, but it has been hypothesized that they are secondary to lung hypoplasia, which is a known feature of Down syndrome.

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