Letter to the Editor

Subpleural Lung Cysts in Children with Trisomy 21

Dear Editor,

Trisomy 21 is a common chromosomal disorder with an incidence of 1 in 750 live births. Many factors contribute to disorders of the respiratory system in children with trisomy 21, and these include structural abnormalities of the airways and lungs, recurrent lower respiratory tract infections and obstructive sleep apnoea.[1]

Cystic lung disease in children with trisomy 21 was first described in 1986 by Joshi et al from the autopsy findings of 2 infants with lung cysts and congenital heart disease.[2] A later study in 1991 on autopsies of children with trisomy 21 showed a 20% prevalence for subpleural cysts[3] and they were more frequent in children with congenital heart disease. They are difficult to pick out on chest radiographs.[4] Chest computed tomography (CT) is more sensitive in detecting these cysts. Biko et al found a prevalence of 36% for subpleural cysts amongst 25 children with trisomy 21 who underwent CT scanning.[5] The clinical impact of subpleural cysts in children with trisomy 21 is still uncertain. This study aimed to investigate the appearances of subpleural cysts on CT scans of children with trisomy 21, and any associated clinical morbidity.

Materials and Methods

We conducted a retrospective review of the medical notes and radiology results of all children with trisomy 21 (aged under 18 years) attending outpatient clinics and inpatient wards at a tertiary university hospital in Singapore over a 5-year period (from January 2011 to December 2015). Patient details obtained included age, gender, prematurity, coexisting congenital heart disease and any history of respiratory illness, other comorbidities, and prolonged ventilation or extracorporeal membrane oxygenation (ECMO) therapy. Prematurity was defined as <37 weeks of gestation and prolonged ventilation as >21 days of mechanical ventilatory support.[6]

Chest CT scans were performed with high resolution reconstruction. Scans were reported independently by a consultant radiologist and paediatric pulmonologist. Children with CT scans repeated at a later date had their scans analysed for changes in location and size of cysts. Scans were performed on a multidetector CT system with tube current adjusted for each child's age and size. Subpleural cysts were defined as small cystic dilatations along the lung surface. They were defined according to location. Coexisting abnormal CT findings were also described.

The study was approved by the hospital's research ethics committee.

Results

Forty-eight children with trisomy 21 were identified during the study period. Thirteen children underwent chest CT scans. Age range was 2 weeks to 8 years (median 18 months) at the time of CT scanning. Eight children underwent CT scanning following bilateral diffuse airspace changes on their chest X-rays. Two children underwent CT scans to investigate recurrent pneumonia. One child underwent CT scanning of the chest to investigate a persistent stridor from birth while another went for necrotising pneumonia. One child had CT scan to investigate an acute pulmonary hypertensive crisis.

Of the 13 children, 10 had subpleural cysts on CT scanning while cysts were absent in the other 3. For each child, there was complete agreement on the presence or absence of subpleural cysts by the 2 reporters.

Table 1 shows the demographic and clinical characteristics of the children with subpleural cysts. None required ECMO.

Table 2 describes the distribution of subpleural cysts. Eight of the 10 children with subpleural cysts (80%) had cysts along the bronchovascular bundles. Four children (40%) had fissural cysts, predominantly in the oblique fissure, and with significant sparing of the horizontal fissure. Four children (40%) had intraparenchymal cysts (Fig. 1).

Two children underwent repeat chest CT scans 2 years after the first scans. Both children had evidence of new cyst development in follow-up scans. The first scans in these children were done at 2 years 11 months and 8 years 3 months of age, respectively. These new cysts were located in the posterior and basal areas of the lung in both children. Increase in the sizes of the apical and anterior cysts were also noted in both children.

Interstitial lung disease was reported in the CT scans of 2 children with subpleural cysts (20%). One child had findings of ground glass opacities in both lungs, suggesting lung fibrosis. The child did not undergo any further investigations

Table 1. Clinical Characteristics and Demographic Details of Patients

Patient (Gender)	Age at CT Diagnosis	Gestation	Coexisting Congenital Heart Disease	History of Prolonged Ventilator Support (>21 Days)	History of Recurrent Respiratory Infections	Pulmonary Hypertension	Other Comorbid Conditions
Patient 1 (female)	2 weeks	Term	VSD, ASD, PDA, bicuspid aortic arch	Yes (from birth for 74 days)	No	Yes (post-VSD repair)	Stridor from innominate artery compression on trachea, GORD
Patient 2 (male)	4 months	36 weeks	AVSD	No	No	No	None
Patient 3 (female)	6 months	Term	ASD, PDA	No	Yes (mainly ventilator-associated pneumonia)	Yes (severe refractory pulmonary hypertension after viral URTI)	Intrahepatic vascular malformation (involving left portal vein with hepatomegaly), Grade 1 IVH, subclinical hypothyroidism, GORD
Patient 4 (male)	8 months	Term	PDA	No	No	No	Hypothyroidism, GORD
Patient 5 (male)	10 months	Term	TOF	No	No	No	Hypospadias, reactive airways disease, Grade 1 vesico-ureteric reflux bilaterally
Patient 6 (male)	1 year 5 months	Term	TOF	No	Yes (recurrent aspiration pneumonia)	No	Bilateral cleft lip and palate, hiatus hernia with GORD
Patient 7 (male)	1 year 7 months	Term	ASD, mild left pulmonary artery stenosis	Yes (necrotising pneumonia)	Yes (recurrent community-acquired pneumonia)	Yes (following necrotising pneumonia)	Imperforate anus, OSA
Patient 8 (male)	2 years 2 months	Term	AVSD	No	Yes (recurrent aspiration pneumonia)	Yes (post-AVSD repair)	Swallowing dysfunction, severe GORD
Patient 9 (female)	2 years 11 months	Term	None	No	No	No	GORD, OSA
Patient 10 (female)	8 years 3 months	Term	None	No	No	No	OSA

ASD: Atrial septal defect; AVSD: Atrioventricular septal defect; CT: Computed tomography; GORD: Gastroesophageal reflux disease; IVH: Intraventricular haemorrhage; OSA: Obstructive sleep apnoea; PDA: Patent ductus arteriosus; TOF: Tetralogy of Fallot; URTI: Upper respiratory tract infections; VSD: Ventricular septal defect

Table 2. Distribution of Subpleural Cysts on Chest CT Scans in Children with Trisomy 21 at the Time of Diagnosis of Subpleural Cysts

Patient (Gender)	Distribution of Subpleural Cysts
Patient 1 (female)	Right-sided, anteriorly located
Patient 2 (male)	Bilateral, posteriorly located
Patient 3 (female)	Bilateral, anterior and posteriorly located
Patient 4 (male)	Bilateral, anterior and posteriorly located
Patient 5 (male)	Left-sided, laterally located
Patient 6 (male)	Left-sided, posteriorly located
Patient 7 (male)	Bilateral, anterior and posteriorly located
Patient 8 (male)	Bilateral, posteriorly located
Patient 9 (female)	Bilateral, anterior and posteriorly located
Patient 10 (female)	Bilateral, anterior and posteriorly located

CT: Computed tomography

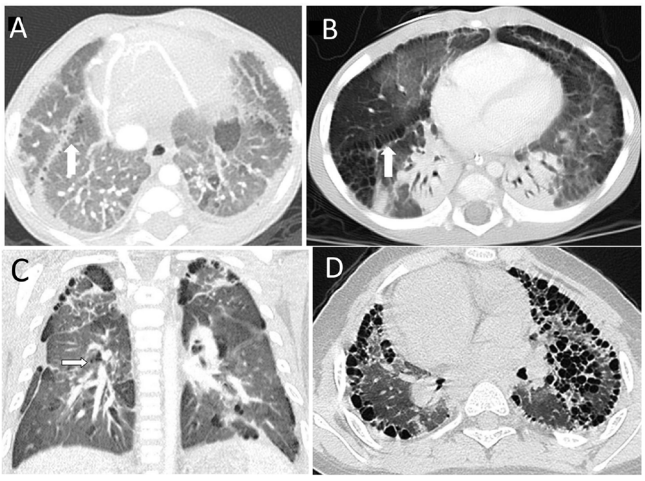

Fig. 1. Subpleural cysts in children with trisomy 21. A) Fissural cysts (white arrows) in a female aged 6 months and B) a male aged 1 year and 7 months. C) Bronchovascular cysts (white arrow) in a male aged 8 months. D) Parenchymal cysts within the left lung of a female aged 2 years and 11 months.

as he remained clinically well from a respiratory standpoint, but he remains under close follow-up for any respiratory symptoms of concern. The other child had findings of coarse reticular pattern in both lungs on the initial scan, suggesting lung fibrosis, but these appearances resolved on a subsequent scan (despite an increase in the sizes of subpleural cysts). None of the 10 children with subpleural cysts had signs of pulmonary hypertension, changes in the pulmonary vasculature, or pleural thickening. The child who was investigated for pulmonary hypertension had dilated pulmonary arteries consistent with pulmonary arterial hypertension but did not have subpleural cysts.

Discussion

Subpleural cysts exist in children with trisomy 21, but are rarely found in non-trisomy 21 children.[7] The origins of these cysts are not entirely clear, but may be related to alveolar hypoplasia in trisomy 21.[2,3,8] Reported histological examinations of the lungs of children with trisomy 21 demonstrated reduced alveolar numbers, increased alveolar size, and deficiency of elastic fibres in the entrance rings to the alveoli.[9] These processes may result in cyst development in the postnatal period during the time of continued alveolar growth, hence their subpleural location. Cysts were much more likely to be found beyond the first month.[3] We found that cysts can increase in size with time, and new cysts can continue developing even in children up to 10 years of age, suggesting that the appearance of cysts can change during childhood.

There were suggestions that subpleural cysts developed from ischaemic tissue damage and compression of bronchi and small airways, presumedly related to congenital heart disease, left-to-right shunting and subsequent compression of bronchi by enlarged arteries and small airways by interstitial fluid.[3,10] However, children with congenital heart disease in the absence of trisomy 21 do not normally manifest with subpleural cysts, so this cannot completely explain the pathogenesis of subpleural cysts. Nevertheless, we found that most of our children with subpleural cysts had coexisting congenital heart disease, although this could be a reflection of children with heart disease who were more likely to have undergone chest CT scans, and therefore, more likely to have subpleural cysts revealed.

Tyrrell et al suggested that subpleural cysts were associated with increased mortality and morbidity from congenital heart disease in children with trisomy 21.[7] This has been postulated due to the presumed earlier than expected death in their case, and a higher incidence of pulmonary hypertension in Gonzalez et al's postmortem series.[3] They also proposed an altered postoperative course in these children, with subpleural cysts reducing gas exchange surface area, and altering lung mechanics making ventilation less effective. In our study, only 2 of 5 children who underwent cardiac operations needed prolonged ventilation postoperatively. We could not demonstrate a clear association with pulmonary hypertension; only 3 children with subpleural cysts (30%) had evidence of pulmonary hypertension by echocardiography.

We demonstrated some consistent features with regard to subpleural cyst location. Although most of the children had cysts in the posterior and basal regions, the cysts can be present in any part of the lungs. New cysts tended to appear in the posterior and basal regions on subsequent CT scans. Fissural cysts were confined to the oblique fissure. The reasons for these patterns of distribution were not clear.

There are limitations to our study. Due to the small number of patients in our series, a definitive association between the presence of cysts and comorbid conditions such as prematurity, congenital heart disease and pulmonary hypertension could not be drawn. This is compounded by the fact that it is not possible to know whether children who did not undergo CT scans had subpleural cysts. However, our data does demonstrate that children with trisomy 21 and subpleural cyst do not necessarily have a poor cardiovascular or respiratory outcome.

Conclusion

Subpleural cysts may be a feature of children with trisomy 21. They may be present in any location in the lungs, but subsequent new cyst development tend to be in the posterior and basal regions. They are not necessarily associated with significant cardiac or respiratory morbidity. These cysts can increase in size over time, with the development of new cysts occurring at any stage of childhood.

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