Hypoxaemia and interstitial lung disease in an infant with hypothyroidism and hypotonia

Dawn Simon, *Emory University*
Ajay Kasi, *Emory University*
MM Lynn, *Emory University School of Medicine*

Journal Title: BMJ Case Reports

Volume: Volume 13, Number 12

Publisher: (publisher) | 2020-12-22

Type of Work: Article

Publisher DOI: 10.1136/bcr-2020-238466

Hypoxaemia and interstitial lung disease in an infant with hypothyroidism and hypotonia

Melodie M Lynn,[1] Dawn Simon,[2] Ajay S Kasi [2]

[1]Pediatrics, Emory University School of Medicine, Atlanta, Georgia, USA
[2]Pediatric Pulmonology, Emory University School of Medicine, Atlanta, Georgia, USA

Correspondence to
Dr Ajay S Kasi;
ajay.kasi@emory.edu

Accepted 30 November 2020

To cite: Lynn MM, Simon D, Kasi AS. *BMJ Case Rep* 2020;**13**:e238466. doi:10.1136/bcr-2020-238466

SUMMARY

A 7-month-old-term male infant presented with cough, tachypnoea, hypoxaemia and post-tussive emesis. Clinical history was significant for respiratory failure and pulmonary hypertension in the neonatal period requiring assisted ventilation, congenital hypothyroidism, mild hypotonia, recurrent respiratory infections, hypoxaemia requiring supplemental oxygen and nasogastric tube feeds. Physical examination showed tachypnoea, coarse bilateral breath sounds and mild hypotonia. Chest radiograph revealed multifocal pulmonary opacities with coarse interstitial markings and right upper lobe atelectasis. Following antibiotic therapy for suspected aspiration pneumonia, chest CT scan was performed and showed multiple areas of pulmonary consolidation and scattered areas of bilateral ground-glass opacities. Genetic studies showed a large deletion of chromosome 14q13.1–14q21.1, encompassing the NK2 homeobox 1 (*NKX2-1*) gene consistent with a diagnosis of brain–thyroid–lung (BTL) syndrome. Our case highlights the importance of genetic studies to diagnose BTL syndrome in infants with hypothyroidism, hypotonia and lung disease.

BACKGROUND

Childhood interstitial lung disease (ILD) is a group of rare respiratory disorders in children manifested by persistent respiratory symptoms and signs such as cough, tachypnoea, crackles, chest retractions and digital clubbing along with hypoxaemia and diffuse pulmonary abnormalities on chest imaging.[1 2] Due to the rarity of childhood ILD and presentation with non-specific symptoms and signs, the diagnosis is often delayed.[1] Brain–thyroid–lung (BTL) syndrome is a rare genetic disorder due to deletions or pathogenic variants in the NK2 homeobox 1 (*NKX2-1*) gene that is associated with ILD. The incidence and prevalence of BTL syndrome is unknown.[3] The clinical course is variable, and progressive respiratory failure due to chronic ILD and pulmonary hypertension can lead to death.[4 5]

We report a 7-month-old boy with BTL syndrome with hypothyroidism, hypotonia, recurrent respiratory infections and hypoxaemia due to ILD. Clinicians should maintain a high index of suspicion for BTL syndrome in children with hypotonia, hypothyroidism and lung disease. Due to progressive lung disease and potentially fatal outcomes associated with this disease, early diagnosis and close clinical monitoring may improve outcomes.

CASE PRESENTATION

A 7-month-old male infant with congenital hypothyroidism and mild hypotonia on home oxygen therapy presented with cough, post-tussive emesis and tachypnoea. There was no history of wheezing, fever, coughing or choking with feeds. In the emergency department, he was afebrile, tachypnoeic with a respiratory rate of 55/min, and oxygen saturation was 88% on 0.25 L/min oxygen. Examination also revealed coarse bilateral breath sounds, mild hypotonia and mild neurodevelopmental delay. Nasal cannula oxygen was increased to 1 L/min that led to improved oxygen saturation and he was hospitalised for further management.

He was born at term by an uncomplicated Cesarean section and developed respiratory distress in the delivery room requiring hospitalisation in the neonatal intensive care unit. Physical examination at birth showed tachypnoea, chest retractions and mild hypotonia. Chest radiograph at birth showed a right tension pneumothorax requiring needle decompression and chest tube placement. Due to progressive respiratory failure, he required intubation and mechanical ventilation. An echocardiogram at birth showed moderate pulmonary hypertension. The newborn screen was concerning for congenital hypothyroidism with low thyroxine and normal thyroid stimulating hormone which were confirmed with additional testing. However, ultrasound of the thyroid was not performed. At 4 weeks of age, due to inability to wean off oxygen, he was discharged home on nasal cannula oxygen at 0.25 L/min and levothyroxine. Subsequently, there were several hospitalisations during infancy for recurrent respiratory infections when he presented with tachypnoea, respiratory distress and hypoxaemia requiring increased oxygen supplementation. At 3 months of age, chronic pulmonary aspiration was clinically suspected and nasogastric tube feeds were initiated. Despite nasogastric tube feeds, cough, intermittent tachypnoea, scattered crackles and oxygen requirement persisted during routine outpatient clinic visits.

INVESTIGATIONS

Chest radiograph showed multifocal pulmonary opacities with coarse interstitial markings and right upper lobe atelectasis (figure 1). Complete blood counts and serum electrolytes were normal. Nasopharyngeal swab for respiratory viral panel by PCR and blood culture resulted negative. Echocardiogram was normal with resolved pulmonary hypertension. A videofluoroscopic swallow study demonstrated aspiration with thin and nectar thick liquids, for

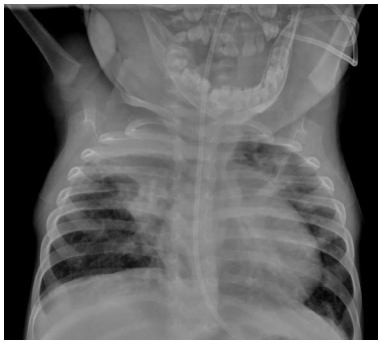

Figure 1 Chest radiograph demonstrates multifocal pulmonary opacities with coarse interstitial markings and right upper lobe atelectasis. A feeding tube is partially visualised.

which continued nasogastric tube feeds were recommended. Following clinical recovery, chest CT scan was performed and showed multiple areas of pulmonary consolidation and scattered areas of bilateral ground-glass opacities (figure 2). Due to persistent mild hypotonia and neurodevelopmental delay, he was evaluated by the neurologist and a brain MRI was performed which was normal. Subsequently, chromosomal microarray analysis showed a large deletion of 14q13.1–14q21.1 encompassing the *NKX2-1* gene consistent with a diagnosis of BTL syndrome.

DIFFERENTIAL DIAGNOSIS

In an otherwise healthy infant, an acute presentation with cough, tachypnoea, post-tussive emesis and hypoxaemia likely suggests a respiratory infection. A lower respiratory tract infection such as bronchiolitis or pneumonia is generally considered in the differential diagnosis. Foreign body aspiration should be on the differential when there is acute cough and dyspnoea even if the typical history of aspirating a foreign body cannot be elicited. Congestive cardiac failure can also be suspected in children with a similar presentation. In our patient with hypotonia, neurodevelopmental delay, and feeding dysfunction, aspiration lung disease should be considered. Recurrent respiratory infections due to underlying immunodeficiency or congenital lung abnormalities are also a possibility. In children with chronic hypoxaemia, differential diagnoses include disorders leading to ventilation–perfusion mismatch, hypoventilation, right-to-left shunts and diffusion impairment. ILD should be suspected in a child with persistent respiratory symptoms and signs such as tachypnoea, cough, chest retractions, crackles accompanied by hypoxaemia and diffuse pulmonary abnormalities on chest radiographs or CT scan.[1 2] The constellation of clinical features including hypotonia, hypothyroidism and lung disease prompted genetic studies that confirmed the diagnosis of BTL syndrome.

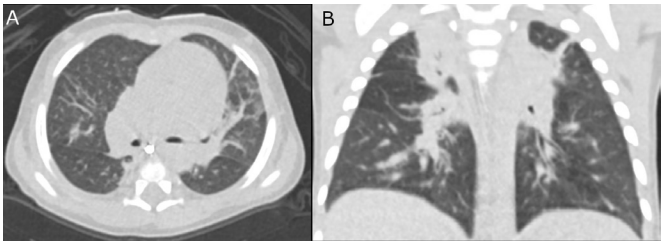

Figure 2 Chest CT (A) axial and (B) coronal sections show ground glass opacities and patchy pulmonary consolidations.

TREATMENT

During the hospitalisation, our patient was treated with amoxicillin–clavulanate for suspected aspiration pneumonia and intravenous fluids. Once emesis had resolved, nasogastric tube feeds were resumed, and supplemental oxygen was weaned with continuous pulse oximetry monitoring. He was discharged home on nasogastric tube feeds and supplemental oxygen by nasal cannula at 0.25 L/min.

OUTCOME AND FOLLOW-UP

At 14 months of age, he was again hospitalised with respiratory distress and hypoxaemia. Chest radiograph showed chronic pulmonary interstitial opacities and patchy areas of atelectasis. Serum bicarbonate was elevated at 34 mmol/L. Capillary blood gas showed pH of 7.36 and partial pressure of carbon dioxide (P_{CO2}) of 60 mm Hg suggestive of compensated respiratory acidosis. He was subsequently diagnosed with chronic respiratory failure and nocturnal bilevel positive airway pressure (BPAP) therapy via nasal mask was initiated for ventilatory support that resulted in improved oxygenation and ventilation. He was discharged home on BPAP during sleep and nasal cannula oxygen during the day. Parental genetic studies and genetic counselling were recommended due to the familial inheritance pattern reported in some cases. Neurology follow-up was established to monitor developmental delays and for any early signs of movement disorders. Follow-up appointments with endocrinology for hypothyroidism, gastroenterology for management of nasogastric tube feeds, genetics and pulmonology were also established.

DISCUSSION

BTL syndrome is a rare genetic disorder due to deletions or pathogenic variants in the *NKX2-1* gene.[1] Thyroid transcription factor 1, which is encoded by the *NKX2-1* gene plays an important role in the development of the thyroid, central nervous system (CNS) and lungs.[6] BTL syndrome is inherited in an autosomal dominant inheritance pattern and some de novo cases have been reported.[3 6] Patients generally present during the neonatal period, infancy or early childhood with non-specific hypotonia or developmental delay, hypothyroidism, neonatal respiratory distress with or without pulmonary hypertension, recurrent respiratory infections and/or ILD.[1 4 7] Affected individuals may have variable degrees of neurological, thyroid and lung disease and may not manifest all the clinical features of BTL syndrome.[3–5] Studies have shown that only around 50%–57% of patients with *NKX2-1* gene abnormalities may manifest the full triad of BTL syndrome.[4 5 7] Other neurological features include chorea, motor or cognitive delay, ataxia and gait impairment. Chorea generally presents around 2–3 years of age.[8] Some children with hypothyroidism are diagnosed at birth when identified on the newborn screening, whereas a few children may be diagnosed during infancy or childhood requiring thyroid hormone replacement therapy. Ultrasound of the thyroid may reveal either normal morphology, thyroid hypoplasia or rarely athyreosis.[5] Therefore, we have recommended this study for our patient.

The *NKX2-1* gene regulates surfactant homeostasis and is a transcription factor for surfactant proteins.[1] Lung disease ensues from surfactant dysfunction and disrupted lung development. Children can present either during the neonatal period, infancy or childhood with a variety of respiratory problems such as neonatal respiratory distress syndrome, recurrent respiratory infections and/or ILD.[4 7] Progressive respiratory failure from chronic ILD and pulmonary hypertension can lead to death.[4 5] Respiratory examination findings may include tachypnoea, chest

retractions, nasal flaring, crackles and wheezing. Failure to thrive (FTT) has been reported in children with ILD.[7] Chest radiograph may show diffuse pulmonary abnormalities or hazy opacities.[6 9] Chest CT findings include pulmonary ground glass opacities, cysts, consolidations and/or architectural distortion.[7 9] During the evaluation of suspected childhood ILD, surgical lung biopsy may be required to diagnose ILD in cases where less invasive tests fail to confirm a diagnosis.[1] *NKX2-1* genetic tests may lead to the accurate diagnosis of BTL syndrome and obviate the need for a surgical lung biopsy, as described in our patient.[2] In cases where a lung biopsy is performed, lung histological abnormalities are variable and include septal thickening, accumulation of foamy alveolar macrophages, hyperplasia of alveolar type II cells and alveolar growth abnormalities.[4 7 9] Lung disease may be the only manifestation in some children prior to the onset of thyroid or neurological abnormalities. The variable clinical features and ages at presentation may render the diagnosis of BTL syndrome challenging, and often delay an accurate diagnosis.[4] Our patient presented with the full triad of BTL syndrome—neonatal respiratory distress with persistent hypoxaemia and ILD, hypotonia and congenital hypothyroidism that led to the diagnosis.

The mechanisms for variable phenotypes and severity of lung disease in children with BTL syndrome are unknown. Patients with large deletions had lung, thyroid and CNS abnormalities as well as early onset disease, as seen in our patient. Since an autosomal dominant inheritance pattern has been reported, genetic testing of the parents may be indicated to detect familial cases and to determine recurrence risk.[4]

Currently, there are no specific treatments for children with BTL syndrome. Thyroid hormone replacement therapy is indicated in children with hypothyroidism.[3] Although optimal medications for treatment of chorea related to BTL syndrome are unknown, several medications such as levodopa, clonazepam and tetrabenazine have been used.[8] The treatment of lung disease remains supportive. Supplemental oxygen and non-invasive positive pressure ventilation have been used in children with hypoxaemia or chronic respiratory failure.[4 7] Lung transplantation has been performed in patients with advanced lung disease and respiratory failure.[3 4 7] Muscular hypotonia causes difficulty in clearing airway secretions, thereby increasing susceptibility to atelectasis and respiratory infections. In children with hypotonia, chest physiotherapy could be beneficial to promote secretion clearance.[3] In children at risk for aspiration or with FTT, close attention to nutrition and a feeding tube may be required. Complications of nasogastric tube feeding include obstruction of the nostril, gastro-oesophageal reflux and potential migration into the lower airway.[3] Therefore, gastrostomy tube feeding may be preferable. Avoiding exposure to sick contacts, routine childhood immunisations including influenza vaccine, and in some cases, immunoprophylaxis against respiratory syncytial virus may reflect strategies to prevent recurrent respiratory infections.[2 4]

Learning points

- Respiratory disease in a child with hypothyroidism, hypotonia or chorea should prompt clinicians to consider a diagnosis of brain–thyroid–lung syndrome and referral to a paediatric pulmonologist.
- Clinicians should consider a diagnosis of interstitial lung disease in a child with persistent respiratory symptoms, abnormal pulmonary examination, hypoxaemia and diffuse abnormalities on chest imaging.
- Children with brain–thyroid–lung syndrome require comprehensive multidisciplinary care to optimise medical management and improve outcomes.

Acknowledgements The authors thank the patient and his parent for their participation in this report.

Contributors Patient was under the care of DS and ASK. Report was written by all authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Ajay S Kasi http://orcid.org/0000-0003-0435-2807

REFERENCES

1 Spagnolo P, Bush A. Interstitial lung disease in children younger than 2 years. *Pediatrics* 2016;137:e20152725.
2 Kurland G, Deterding RR, Hagood JS, *et al*. An official American thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. *Am J Respir Crit Care Med* 2013;188:376–94.
3 Wilmott RW, Deterding R, Li A, *et al*. *Kendig's Disorders of the Respiratory Tract in Children*. 9th edn. Philadelphia, PA: Elsevier, 2019.
4 Hamvas A, Deterding RR, Wert SE, *et al*. Heterogeneous pulmonary phenotypes associated with mutations in the thyroid transcription factor gene NKX2-1. *Chest* 2013;144:794–804.
5 Carré A, Szinnai G, Castanet M, *et al*. Five new TTF1/NKX2.1 mutations in brain-lung-thyroid syndrome: rescue by Pax8 synergism in one case. *Hum Mol Genet* 2009;18:2266–76.
6 Salerno T, Peca D, Menchini L, *et al*. Respiratory insufficiency in a newborn with congenital hypothyroidism due to a new mutation of TTF-1/NKX2.1 gene. *Pediatr Pulmonol* 2014;49:E42–4.
7 Nattes E, Lejeune S, Carsin A, *et al*. Heterogeneity of lung disease associated with NK2 homeobox 1 mutations. *Respir Med* 2017;129:16–23.
8 Parnes M, Bashir H, Jankovic J. Is Benign Hereditary Chorea Really Benign? Brain-Lung-Thyroid Syndrome Caused by *NKX2-1* Mutations. *Mov Disord Clin Pract* 2019;6:34–9.
9 LeMoine BD, Browne LP, Liptzin DR, *et al*. High-Resolution computed tomography findings of thyroid transcription factor 1 deficiency (NKX2-1 mutations). *Pediatr Radiol* 2019;49:869–75.