Tachypnea of Infancy as the First Sign of Sanfilippo Syndrome

abstract
This report describes the first known case of Mucopolysaccharidosis type IIIA presenting with respiratory symptoms and characteristic lung pathology. This case highlights under-recognized areas of systemic involvement and earlier modes of presentation in lysosomal storage disorders as well as the importance of investigating infants who have persistent tachypnea. Pediatrics 2014;134:e884–e888
Primary lung involvement is a well-recognized feature of several lysosomal storage diseases including Neimann Pick disease type B and Gaucher disease. In the other mucopolysaccharidosis (MPS) disorders, a variety of respiratory manifestations occur; with both upper and lower airway obstruction being prominent late features of MPS I and II. Restrictive lung disease predominates in those who have significant skeletal involvement, such as MPS IV and VI. To our knowledge, this case is the first report of respiratory symptoms and subsequent lung pathology leading to a diagnosis of MPS III, otherwise known as Sanfilippo syndrome.

CASE PRESENTATION

A 37-week-gestation boy was born to consanguineous parents by induced vaginal delivery after an uncomplicated pregnancy. The indication for induction was a previous term stillbirth of unknown etiology. Birth weight was 3160 g and Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. At 10 minutes of life, he started grunting and his oxygen saturation was 80% in room air. Continuous positive airway pressure with 40% oxygen was initiated. Arterial blood gas revealed a pH of 7.45, PCO2 of 42, and bicarbonate of 23. A chest radiograph showed a bilateral, diffuse ground-glass appearance. At 36 hours of life he was intubated and ventilated owing to worsening respiratory distress. On day 5 of life, he was transferred to a tertiary level NICU for further management. He received 3 doses of surfactant with minimal improvement. Infectious workup was negative. An echocardiogram performed on the seventh day of life revealed good biventricular function, no right ventricular dilatation, mild septal flattening in diastole, and a patent foramen ovale that showed blood flow shunting from left to right. He failed extubation once before being successfully extubated to nasal continuous positive airway pressure on day 13 of life. A chest computed tomography (CT) scan revealed diffuse bilateral ground-glass opacifications (Fig 1A). The unexplained term neonatal respiratory distress prompted genetic testing for surfactant deficiency. Gene sequence analysis of Adenosine Triphosphate-Binding Cassette protein member A3 (ABCA3) revealed 2 sequence variants of unknown significance in p.T385A and c.4165-8G>A. His asymptomatic father was later shown to carry the same variants. No mutations were found with gene sequence analysis of surfactant protein B or C.

Over the course of several weeks, the infant was successfully weaned off supplemental oxygen. However, persistent tachypnea (respiratory rate of 60 to 70 per minute) and increased work of breathing (intercostal in-drawing) with feeding difficulty remained. He was discharged from the hospital at 2 months of age.

At 4 months of age, the infant was readmitted to hospital for feeding difficulties and failure to thrive (weight and height below third percentiles). He remained tachypneic (respiratory rate over 60 breaths per minute) but was able to maintain normal oxygen saturations. A metabolic screen, including serum amino acids, urine amino acids, and urine organic acids, did not detect any abnormalities. A sweat chloride test was negative and serum immunoglobulins were within normal limits. A repeat chest CT revealed patchy ground-glass opacification in both lungs centrally and focal emphysematous changes in the medial aspect of both lower lobes (Fig 1B).

A lung biopsy was performed at 5 months of age. Light microscopy showed no evidence of an inflammatory process and normal septal wall thickness but did reveal diffuse over-expansion of alveolar spaces owing to deficient alveolarization, similar to cases of post surfactant bronchopulmonary dysplasia (Fig 2A). Electron microscopy identified interstitial cells with vacuolated cytoplasm and flocculent substrate suggestive of a mucopolysaccharide substance (Fig 2B and C). Type II pneumocytes were found to have normal ultrastructure with no evidence of abnormal lamellar bodies.

A metabolic assessment for storage disease was then performed; thin-layer chromatography for urine mucopolysaccharides showed an increased excretion of heparan sulfate, suggestive of MPS III. Enzymatic testing was consistent with a diagnosis of MPS IIIA with deficient heparan sulfamidase activity at 0 nmoles/mg protein/17 h (NR 25–75). Genetic testing confirmed the diagnosis with homozygous mutations in the SGSH gene (p.R74H).

At 2 years of age, the boy is well, with resolution of his feeding issues and tachypnea, adequate growth (weight and height at the 50th to 75th percentiles), appropriate verbal, motor, and social developmental milestones, and normal neurologic examination. The only stigmata of his devastating diagnosis are...
subtle coarse facial features, including prominent eyebrows and supra-orbital ridge, and an umbilical hernia. A recent chest radiograph shows persistent increased interstitial lung markings, which are less pronounced than previous imaging, in keeping with mild interstitial lung disease (Fig 3).

**DISCUSSION**

MPS III, also known as Sanfilippo syndrome, is an autosomal recessive lysosomal storage disease resulting in mucopolysacchariduria and accumulation of glycosaminoglycan heparan sulfate in the tissues. Compared with other mucopolysaccharidoses, the central nervous system appears to be the major organ affected in MPS III. MPS III has 4 variants, based on the respective deficiency of the catalytic enzymes, which all lead to the same phenotype: MPS IIIA (heparin N-sulphatase), MPS IIIB (α-N-acetylglucosaminidase), MPS IIIC (acetyl-coenzyme A: α-glucosaminide acetyltransferase), and MPS IIID (N-acetylglucosamine 6-sulfatase).

In the majority of patients who have MPS IIIA, the first signs and symptoms of disease appear at 2 to 3 years of age, with a median age of diagnosis of 4.5 years. Initial symptoms consist of developmental delay (primarily speech) and/or behavioral problems (hyperactivity, aggression, or destructive behavior). Progressive mental deterioration eventually culminates in severe dementia and death by a median age of 18 years. Other medical problems include hearing and vision abnormalities, seizures, diarrhea, and sleep disturbances. Respiratory disease is not reported in association with MPS III.

The typical clinical phenotype of MPS IIIA was not displayed in this case, likely owing to his unusually young age at diagnosis. His initial symptoms were primarily respiratory. The simplified, over-expanded alveoli evident on lung biopsy could potentially be attributed to MPS and its deleterious effects on lung development, and may have influenced the clinical presentation. It is also possible that the compound heterozygous ABCA3 mutations found in our patient may have contributed to his respiratory symptoms. ABCA3 plays a role in surfactant lipid transport into lamellar bodies, and mutations in this gene have been shown to cause interstitial lung disease owing to surfactant deficiency. The classic lung pathology findings include desquamative interstitial pneumonia-like picture with or without alveolar proteinosis and abnormal lamellar bodies with dense inclusion bodies observed on electron microscopy, which were not evident in our case. Lung disease caused by ABCA3 mutations requires mutations in both alleles as it is inherited as an autosomal recessive disorder. The ABCA3 sequence variants in our patient were likely not disease-causing, as his unaffected father was shown to carry the same variants. However, previous studies have shown that heterozygous ABCA3 mutations can modify the severity of lung disease associated with surfactant protein C mutations. Single ABCA3 mutations have also been found to increase the risk for neonatal respiratory distress syndrome in infants 34 weeks’ gestation and older. It is therefore plausible that heterozygous ABCA3 mutations may sufficiently exacerbate lung disease.

![Figure 2](image1.png)

**FIGURE 2**
A, Light microscopy view of open lung biopsy showed diffuse over-expansion and simplification of alveolar spaces (asterisk) with well-preserved lung parenchyma including small bronchioles (Br) and pulmonary arteries (PA) with no evidence of septal wall thickening. B, Low magnification EM view of lung biopsy showed interalveolar septum delineated by alveolar spaces (Alv), some with alveolar type 2 cells (white arrow) containing several vacuolated interstitial storage cells (asterisk) characteristic of MPS. C, Higher magnification of interstitial storage cells, some with nucleus (n) and cytoplasm filled with mucopolysaccharide appearing as empty spaces owing to extraction (asterisk). Interstitial collagen (Col).

![Figure 3](image2.png)

**FIGURE 3**
Chest radiograph at 2 years of age with persistent increased interstitial lung markings.
associated with mucopolysaccharide deposition to produce clinically apparent respiratory symptoms. Currently all the MPS disorders remain incurable, but a variety of therapies have become available in the last decade. These include exogenous enzyme replacement therapy, with phase II trials completed for MPS IIIA, and other specific therapies under development. Maximal therapeutic benefit will likely require early diagnosis and treatment initiation. This case demonstrates that respiratory symptoms may herald the diagnosis of MPS III before neurologic deterioration.

It is imperative that any infant who has chronic tachypnea and diffuse parenchymal abnormalities on lung imaging have prompt and appropriate investigations to help elucidate an etiology (Table 1). In this case, flexible bronchoscopy with bronchoalveolar lavage was not performed but is usually recommended to exclude infection or airway abnormalities as possible causes of diffuse lung disease. Lung biopsy, although invasive, should be considered for those in whom the diagnosis is uncertain. In particular, electron microscopy should be part of routine handling for all pediatric lung biopsies, as ultrastructural studies play a significant role in the diagnosis of respiratory disorders in young children. Furthermore, all metabolic storage diseases, including MPS IIIA, should be included in the differential diagnosis of diffuse lung disease. Infants should be carefully examined for features of metabolic storage diseases (including coarse facial features and hepatosplenomegaly) and, if present, consultation with a metabolic specialist should be requested to guide further investigations, such as urine for mucopolysaccharidosis.

TABLE 1 Causes of Chronic Tachypnea of Infancy With Diffuse Parenchymal Abnormalities on Lung Imaging

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Potential Informative Investigations</th>
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<tr>
<td>Lung growth abnormalities (including chronic lung disease of prematurity)</td>
<td>Bone scan, bronchoalveolar lavage fluid for cytology, lung biopsy</td>
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<tr>
<td>Neuroendocrine hyperplasia of infancy</td>
<td>Echocardiogram, chest CT, cardiac catheterization, lung biopsy</td>
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<tr>
<td>Pulmonary interstitial glycogenosis</td>
<td>Chest CT, lung biopsy</td>
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<tr>
<td>Surfactant dysfunction disorders</td>
<td>Complete blood count, creatinine, paired plasma/urine amino acids, urine glycosaminoglycans (MPS), disease-specific lysosomal enzymology, abdominal ultrasound, skin biopsy</td>
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<tr>
<td>Hypersensitivity pneumonitis</td>
<td>(electron microscopy/fibroblast culture)</td>
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<td>Eosinophilic pneumonia</td>
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<td>Langerhans cell histiocytosis</td>
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<td>Pulmonary vascular diseases</td>
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<td>Pulmonary lymphatic disorders</td>
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<td>Metabolic storage diseases:</td>
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<td>Gaucher disease</td>
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<td>Niemann Pick disease type B</td>
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<tr>
<td>Mucopolysaccharidosis</td>
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<td>Lysoauric protein intolerance</td>
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REFERENCES

10. Bullard JE, Nogee LM. Heterozygosity for ABCA3 mutations modifies the severity of


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