JIMD Reports
DOI 10.1007/8904_2018_101

RESEARCH REPORT

Neonatal Onset Interstitial Lung Disease as a Primary Presenting Manifestation of Mucopolysaccharidosis Type I

Douglas Bush • Leighann Sremba • Kate Lomax • Jill Lipsett • David Ketteridge • Drago Bratkovic • Yazmin Enchautegui-Colon • James Weisfeld-Adams • Csaba Galambos • Seth Lummus • Eric Wartchow • Jason Weinman • Deborah R. Liptzin • Peter Baker II

Received: 22 November 2017 / Revised: 20 February 2018 / Accepted: 06 March 2018 / Published online: 14 April 2018

Abstract We describe two cases of neonatal onset interstitial lung disease eventually diagnosed as mucopolysaccharidosis type I (MPS I). In both cases, evaluation led to lung biopsy, pathology review, and identification of glycogen deposition. Pulmonary interstitial glycogenosis (PIG) was considered as a clinical diagnosis in case one; however, further review of electron microscopy (EM) was more consistent with MPS I rather than PIG. Both cases were confirmed to have MPS I by enzyme and molecular analysis. Neonatal interstitial lung disease is an atypical presentation for MPS I which is likely under-recognized. Diagnosis through clinical guidelines and a multidisciplinary approach had a major impact on patient management. The diagnosis of MPS I prompted timely initiation of enzyme replacement therapy (ERT) and the patients ultimately underwent hematopoietic stem cell transplantation (HSCT) to improve symptomatic outcomes. In addition to treatment, immediate precautionary recommendations were made to avoid potentially catastrophic outcomes associated with cervical instability. These cases add to the clinical spectrum of MPS I in the newborn period. They further illustrate the difficulties in early recognition of the disease, and importance of a definitive diagnosis of MPS I in infants with interstitial lung disease.

Communicated by: Alberto B. Burlina, MD

Douglas Bush and Leighann Sremba are co-first authors.

D. Bush · D. R. Liptzin
Section of Pulmonary Medicine, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA

L. Sremba · Y. Enchautegui-Colon · J. Weisfeld-Adams · P. Baker II (✉)
Section of Clinical Genetics and Metabolism, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA
e-mail: Peter.BakerIi@ucdenver.edu

K. Lomax · D. Ketteridge · D. Bratkovic
Women's and Children's Hospital, Adelaide, SA, Australia

J. Lipsett · D. Ketteridge · D. Bratkovic
SA Pathology, Women's and Children's Hospital, Adelaide, SA, Australia

C. Galambos · S. Lummus
Department of Pathology and Laboratory Medicine, University of Colorado School of Medicine, Aurora, CO, USA

E. Wartchow
Department of Pathology and Laboratory Medicine, Children's Hospital Colorado, Aurora, CO, USA

J. Weinman
Department of Radiology, University of Colorado School of Medicine, Aurora, CO, USA

Abbreviations

chILD	Childhood interstitial and diffuse lung disease
EM	Electron microscopy
ERT	Enzyme replacement therapy
GAG	Glycosaminoglycan
HSCT	Hematopoietic stem cell transplantation
IDUA	Iduronidase activity
MPS	Mucopolysaccharidosis
PIG	Pulmonary interstitial glycogenosis

Introduction

Mucopolysaccharidosis type I (MPS I) is a lysosomal storage disorder caused by deficiency of α-L-iduronidase with impaired glycosaminoglycan (GAG) degradation and subsequent pathologic accumulation in cell lysosomes in

multiple organs. The prevalence of MPS I is approximately 1/100,000, with a wide phenotypic spectrum (Moore et al. 2008; Beck et al. 2014). Excessive GAG accumulation can lead to growth impairment, joint contractures, neurologic abnormalities, and upper airway obstructive features with progressive cardiopulmonary complications (Berger et al. 2013). Typical respiratory complications are secondary to abnormal upper airway tone, anatomical variations, and GAG deposition in the upper airways with associated sleep disordered breathing (Berger et al. 2013). Less frequently, infraglottic deposition of GAG can contribute to tracheobronchomalacia with associated respiratory distress or related mucous clearance complications (Berger et al. 2013). Rarely, these patients can experience alveolar or interstitial disease impairing gas exchange (Berger et al. 2013) in the newborn period, a disease presentation that is likely under-recognized in MPS I (Kiely et al. 2017).

Historically, the mean age of symptomatic onset in severe MPS I is 6 months, with a mean age of 12 months at formal diagnosis (Beck et al. 2014; Kiely et al. 2017). Earlier recognition of disease affords timely initiation of enzyme replacement therapy (ERT) which has demonstrated promising improvements in 6-min walk distance, pulmonary function testing metrics, and apnea–hypopnea indices in patients with obstructive sleep apnea (Wraith et al. 2004). The median age of starting ERT with recombinant α-L-iduronidase is 18 months (Kiely et al. 2017). Although clinically available, this condition is not yet uniformly screened for by dried blood spot in newborn screening. Notably, ERT has demonstrated improvement in MPS I-associated interstitial lung disease with earlier treatment contributing to improved outcomes (Muenzer et al. 2009). Improvements in cognitive outcomes have been reported in children with MPS I diagnosed and treated with hematopoietic stem cell transplantation (HSCT) prior to 9 months of age (D'Aco et al. 2012; Poe et al. 2014). Successful HSCT implemented early also improves somatic findings including hearing, joint mobility, and cardiopulmonary function (Muenzer et al. 2009; D'Aco et al. 2012; Poe et al. 2014). Cases of early infantile presentation, specifically as interstitial lung disease, are likely under-recognized, and the opportunity for timely intervention is potentially missed. Here, we highlight two cases in which multidisciplinary care and high index of suspicion led to the diagnosis of MPS I, initially presenting as neonatal/infantile interstitial lung disease. Early, confirmatory diagnosis of MPS I had significant and immediate implications for implementation of disease-modifying clinical management decisions.

Case Reports

Case 1

A 36-week-gestation male was born via induced term vaginal delivery after an uncomplicated pregnancy. The patient developed respiratory failure requiring intubation on the first day of life, was extubated on day 4 and had persistent respiratory insufficiency. He was treated for neonatal respiratory distress syndrome with surfactant and antimicrobials. Initial physical exam was notable for tachypnea, retractions, and diffuse, fine crackles throughout all lung fields. Echocardiogram was normal. A chest radiograph demonstrated diffuse granular opacities and follow-up high-resolution chest computed tomography (HRCT) revealed diffuse ground glass opacities bilaterally and scattered thin walled cystic lucencies (Fig. 1a). Flexible bronchoscopy was unremarkable. Bronchoalveolar lavage yielded nonspecific inflammation. The patient was evaluated by Pulmonology for childhood interstitial and diffuse lung disease (chILD) syndrome per American Thoracic Society official clinical guidelines (Kurland et al. 2013), with a working differential that included inherited disorders of pulmonary surfactant dysfunction and pulmonary interstitial glycogenosis (PIG) (Deterding 2010). Extensive evaluation eliminated common causes of diffuse lung disease including aspiration, infection, congenital heart disease, and bronchopulmonary dysplasia. A video-assisted thoracoscopic lung biopsy was performed. Pathologic evaluation of tissue obtained at biopsy revealed areas of alveolar simplification with a thickened interstitial space. Interstitial cells characterized by clear cytoplasm (Fig. 1b) were suggestive of the diagnosis of PIG (Canakis et al. 2002). Periodic acid Schiff staining did not demonstrate increased glycogen content in interstitial cells (not shown). Alcian blue stain highlighted the presence of mucopolysaccharide within these cells (Fig. 1c), and a CD 68 immunostain identified the interstitial cells as macrophages (Fig. 1d). Electron microscopy (EM) revealed prominent accumulation of interstitial cells containing membrane-bound lysosomal inclusions (Fig. 1e) rather than monoparticulate glycogen. Collectively, these findings were consistent with an inherited metabolic storage disorder.

Concurrent with pathologic EM investigation, a clinical workup by Metabolic Genetics was initiated. Urine GAG screening stained strongly positive for Alcian blue with greatly increased heparan sulfate and dermatan sulfate on thin layer chromatography suggestive of MPS types I, II, or VII (Fig. 2a). Enzymatic testing revealed deficient

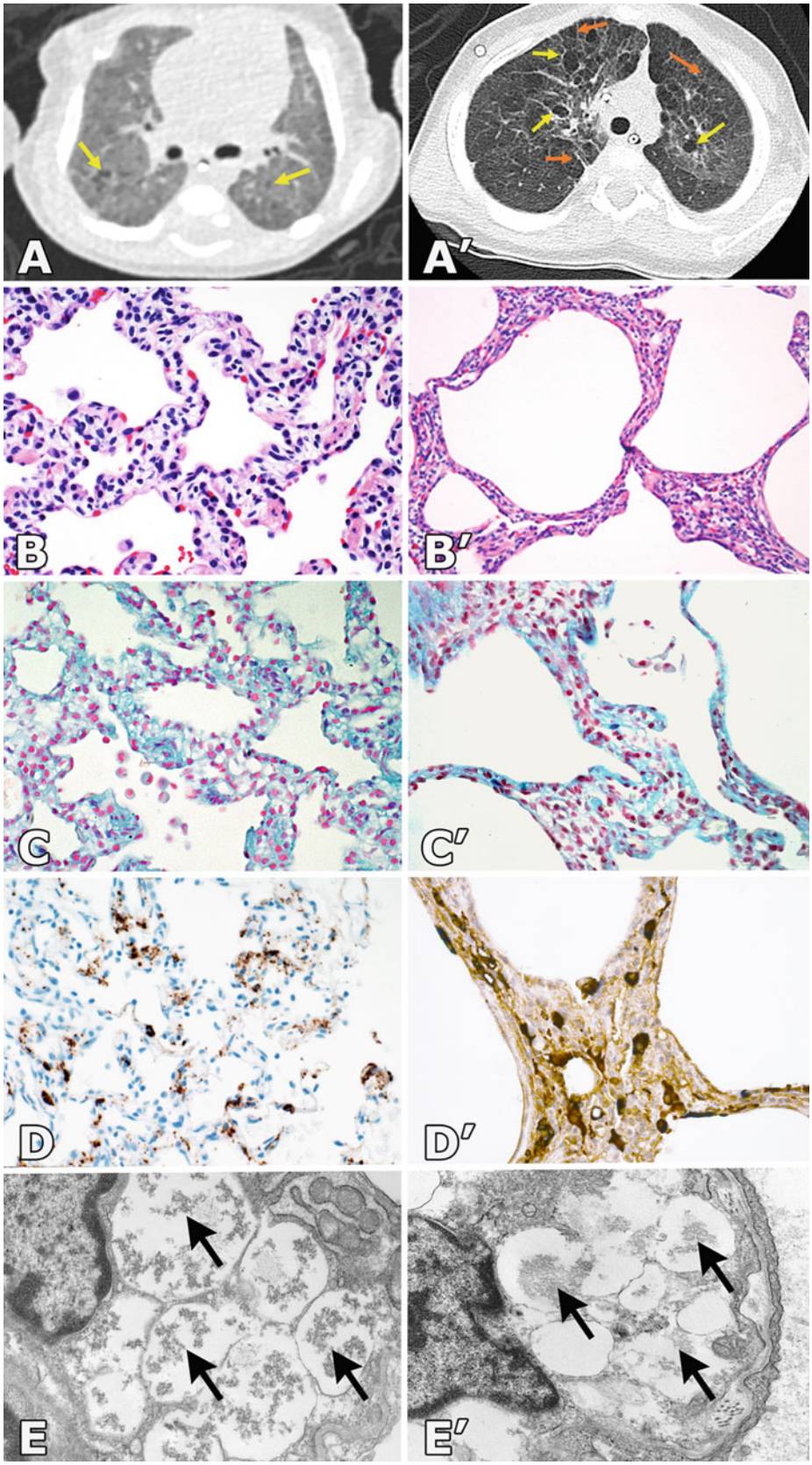

Fig. 1 Imaging, histologic, and ultrastructural findings of both patient 1 (left panel) and patient 2 (right panel) are similar and compared. (**a**, **a**′) Axial non-contrast chest high-resolution chest computed tomography (HRCT) image showing patchy ground glass opacities

α-L-iduronidase activity, confirming the diagnosis of MPS I. Genetic sequencing identified biallelic mutations in the *IDUA* gene, both previously reported and encode premature stop codons (c.208C>T, p.Q70X and c.1205G>A, p.W402X). Physical exam at diagnosis (3 months old) was consistent only with mild dysmorphic features (Fig. 2b). Corneas were clear, and skeletal abnormalities were clinically mild. He had moderate sleep apnea. Skeletal survey confirmed dysostosis multiplex including broadening of the ribs, anterior–inferior beaking of the L2 vertebral body, and tapering of the proximal metacarpals. MRI of the spine demonstrated C1 narrowing due to congenitally small ring and the odontoid process was hypoplastic (Fig. 2c). Mild hepatosplenomegaly on abdominal ultrasound. ERT was initiated and he underwent expedient evaluation for HSCT. He was discharged home at 3 months old with supplemental oxygen and improving growth. General clinical symptoms including respiratory status improved upon starting ERT. Initial unrelated umbilical cord HSCT at 12 months old was complicated by graft rejection and followed by a successful second HSCT at 22 months improving his pulmonary status.

Case 2

A 36-week-gestation male with intrauterine growth restriction was born via caesarian section following a pregnancy complicated by oligohydramnios, maternal hypothyroidism, and gestational diabetes. He developed severe respiratory distress syndrome shortly after birth requiring surfactant administration and initial mechanical ventilation, and subsequently rapidly weaned to continuous positive airway pressure on which he remained until 24 days of life. He transitioned to nasal cannula and was diagnosed with chronic lung disease of unclear etiology. Physical examination initially revealed increased work of breathing which improved with respiratory support and supplemental oxygen. No crackles or wheezes were auscultated and no obvious dysmorphic features were apparent in the first few months of life. No signs of pulmonary hypertension were noted.

Investigations into the etiology of his lung disease included an HRCT chest scan demonstrating diffuse ground glass opacities with areas of air trapping and cyst formation (Fig. 1a′). Genetic testing for surfactant protein abnormalities revealed a heterozygous variant in *ABCA3*; however, this was felt unlikely to be the primary cause of his protracted respiratory symptoms (Wambach et al. 2012). The patient underwent a thoracoscopic lung biopsy with pathologic tissue evaluation at 4 months old. Histology was consistent with abnormal alveolar growth (Fig. 1b′) and patchy inclusions on EM of unclear etiology (Fig. 1e′). As in Case 1, the remainder of the workup was unremarkable. He was given a working diagnosis of chronic cystic and interstitial lung disease of unclear etiology and discharged home at 4.5 months old on supplemental oxygen. At 13 months old, findings of bilateral inguinal hernia and mixed bilateral hearing loss, together with persistent oxygen requirement, prompted MPS screening for urinary excretion of GAG. This returned positive and Metabolic Genetics was consulted. Enzymatic testing revealed deficient α-L-iduronidase and sequencing of *IDUA* identified a homozygous mutation (c.1205G>A, p.W402X), confirming the diagnosis of MPS I. Similar to Case 1, staining of the lung biopsy retrospectively identified the presence of mucopolysaccharide by Alcian blue staining (Fig. 1c′) and lysosome content in interstitial macrophages (Fig. 1d′).

Physical examination at diagnosis (13 months old) revealed moderately coarse, dysmorphic facial features, corneal clouding, bilateral characteristic claw hand deformities, and moderate hepatosplenomegaly. Brain MRI showed communicating hydrocephalus indicative of cervical canal narrowing, and lateral spinal X-ray revealed a gibbus deformity. At 15 months old, ERT was initiated with marked improvement in visceral, soft tissue, and pulmonary symptoms. He underwent initial HSCT at 20 months old. His course was complicated by relapsing respiratory distress.

Discussion

Early MPS I-associated lung disease is an under-recognized disease manifestation that may be present at birth (Berger et al. 2013; Kiely et al. 2017; Valayannopoulos et al. 2010). The patients reported are unique in that the respiratory symptoms were present on day one of life, initiating an evaluation for chILD syndrome (Kurland et al. 2013). Through a high clinical suspicion and a multidisciplinary approach, MPS I was diagnosed by histological and biochemical testing, and confirmed by enzymatic and genetic testing prompting early initiation of ERT with improvement in respiratory status.

Fig. 1 (continued) throughout lungs with thin walled cystic lucencies (yellow arrows) and septal thickening (orange arrows). (**b**, **b′**) Sections of lung biopsies highlight alveolar simplification, thickened interstitial spaces with increased interstitial cells containing clear cytoplasm (H&E, 40×). (**c**, **c′**) Alcian blue stain highlighted increased ground substance material (mucopolysaccharides) within the thickened interstitial spaces at low (20×) and high resolution (40×). (**d**, **d′**) Prominent lysosomal content was observed within the interstitial cells consistent with macrophages (CD68, 40×). (**e**, **e′**) Interstitial cells contained membrane-bound lysosomal inclusions consistent with mucopolysaccharidosis type I (MPS I) (arrows, 25,000×)

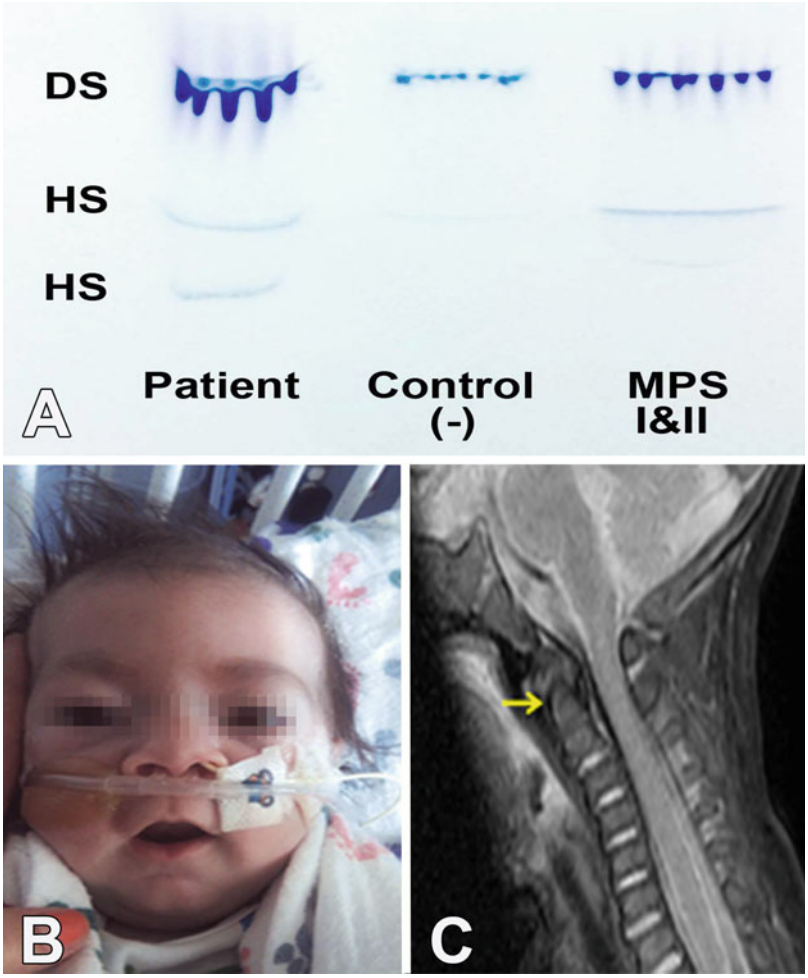

Fig. 2 (**a**) Qualitative urinary glycosaminoglycan (GAG) analysis by multi-solvent sequential thin layer chromatography demonstrating greatly increased dermatan sulfate (DS, dark purple streaks on top band) and heparan sulfate (HS, two faded bands) consistent with a diagnosis of MPS I or II. (**b**) Mild dysmorphic facial features appreciated at 3 months of age with broad nasal root, bulbous nasal tip, flared nostrils, prominent eyebrows, and periorbital fullness. Also note a long philtrum, thin vermillion border, and full appearance of the lower lip (image obtained with written and signed parental consent). (**c**) Sagittal T2 FS MRI cervical spine showing subtle findings of odontoid hypoplasia and narrowing of the spinal canal at C1 and C2 secondary to a congenitally small C1 ring

With efforts to add lysosomal storage disorders to the newborn screen, it has recently been shown that nearly 50% of MPS I affected neonates will have respiratory symptoms in the first month of life (Kiely et al. 2017). This may be much more common than previously recognized. In the largest and most comprehensive study of the natural progression of early symptoms of Hurler syndrome performed at a single center, 25% of subjects required respiratory support of some kind in the neonatal period. However, most pulmonary complications were infectious or upper respiratory, and interstitial lung disease was not listed as a presenting feature (Kiely et al. 2017). Biopsy proven interstitial lung disease as severe as these two case examples, each requiring substantial respiratory support and prolonged hospitalization, has not been widely reported in MPS I.

Another case report, with a neonatal course similar to our two patients, described a child with MPS II diagnosed at 3 years old, after the patient had been previously diagnosed with PIG as an infant (Smets and Van Daele 2011). Review of this report prompted early clinical suspicion for MPS in Case 1. PIG is characterized by an accumulation of non-membrane-bound monoparticulate glycogen distributed diffusely through the cytoplasm (Deutsch and Young 2009). In contrast, EM and appropriate histologic staining in MPS I-related interstitial disease demonstrates membrane-bound GAG within interstitial cell lysosomes. In Case 1, consideration for a metabolic storage substance other than glycogen in our patient with chILD syndrome led to additional clinical evaluation and early diagnosis of MPS I at 3 months old. In Case 2, the diagnosis was made closer to the median age of MPS I

diagnosis, based on a more pronounced evolving clinical phenotype including corneal clouding, coarse facial features, and visceromegaly. Retrospective evaluation of EM imaging (using the lung biopsy performed at 4 months old) was consistent with lysosomal GAG storage. ERT promptly improved clinical features as well as respiratory status.

High suspicion for MPS I and II prompted radiologic investigation with cervical spine MRI in Case 1, which revealed C1 narrowing and odontoid hypoplasia. This potentially catastrophic manifestation of MPS, in the setting of intubation or cervical spine manipulation, poses a risk for spinal cord injury and quadriparesis if precautionary measures are not taken (Pizzutillo et al. 1989; Belani et al. 1993; Hendriksz et al. 2013). Treatment with ERT and HSCT, implemented in both cases, provided clinical benefits in terms of pulmonary and extrapulmonary disease. Early diagnosis and treatment initiation are known to be associated with improved clinical outcomes by standardized measures (D'Aco et al. 2012; Poe et al. 2014). These highly impactful therapeutic and management points warrant consideration of MPS, and thorough investigation of infants with interstitial lung disease. Diagnostic investigations should include a careful review of histology and EM and potentially early, inexpensive, and noninvasive urine MPS screening. With the addition of MPS I to the newborn screen, early detection could lead to even more timely intervention and in turn generally improve patient outcomes and allow for appropriate genetic counseling. These case examples add to the spectrum of pulmonary manifestations found in the natural progression of early symptoms in MPS I.

Synopsis

Neonatal interstitial lung disease is an under-recognized disease manifestation of mucopolysaccharidosis type I (MPS I). We describe two cases of neonatal onset interstitial lung disease initially identified to have glycogen deposition on pathology, although further review of electron microscopy and the clinical phenotype led to a diagnosis of MPS I in both patients.

Details of the Contributions of Individual Authors

Douglas Bush participated in writing the manuscript and was closely involved in the review and revision. Leighann Sremba participated in writing the manuscript with involvement in the continued review and revision. Kate Lomax participated in drafting the clinical description for Case 2, and reviewing and revising the manuscript. Jill Lipsett participated in the clinical and pathology description, and providing pathology specimens for Case 2. David Ketteridge participated in writing and revising the clinical description for Case 2. Drago Bratkovic participated in the clinical and pathology description for Case 2. Yazmin Enchautegui-Colon participated in the metabolic investigations and writing the initial clinical description in Case 1. James Weisfeld-Adams provided clinical care for Case 1 and participated in the review and revision of the manuscript providing genetic and metabolic expertise. Csaba Galambos participated in the pathologic description for both cases, reviewed and revised the manuscript and provided expertise in pathologic diagnosis of PIG. Seth Lummus participated in the pathologic descriptions for both cases, reviewed and revised the manuscript. Eric Wartchow was involved in the initial pathologic description, reviewed and revised the manuscript, provided electron microscopy support, and created figures with legends. Deborah Liptzin wrote the discussion on cHILD syndrome, provided clinical descriptions for PIG, and revised the manuscript. Peter Baker II oversaw the writing and organization of the manuscript, was responsible for the clinical diagnosis of Case 1, participated in multidisciplinary discussions about the manuscript, and reviewed and edited the manuscript.

Peter Baker is the corresponding author and takes full responsibility for the manuscript's content.

Compliance With Ethics and Guidelines

Conflict of Interest

Douglas Bush, Leighann Sremba, Kate Lomax, Jill Lipsett, David Ketteridge, Drago Bratkovic, Yazmin Enchautegui-Colon, James Weisfeld-Adams, Csaba Galambos, Seth Lummus, Eric Wartchow, Jason Weinman, Deborah R. Liptzin, and Peter Baker II declare that they have no conflict of interest.

The authors have not received any honorarium or payment to produce the manuscript. There are no study sponsors involved.

Informed consent was obtained from all patients for which identifying information is included in this chapter.

Prior Abstract Publication/Presentation

Poster presentation at the Society for Inherited Metabolic Disorders annual conference April 3rd, 2016 titled "Evaluation of chILD syndrome leads to early diagnosis of MPS I."

References

Beck M, Arn P, Giugliani R et al (2014) The natural history of MPS I: global perspectives from the MPS I registry. Genet Med 16 (10):759–765

Belani KG, Krivit W, Carpenter BL et al (1993) Children with mucopolysaccharidosis: perioperative care, morbidity, mortality, and new findings. J Pediatr Surg 28(3):403–408. Discussion 408–410

Berger KI, Fagondes SC, Giugliani R et al (2013) Respiratory and sleep disorders in mucopolysaccharidosis. J Inherit Metab Dis 36 (2):201–210

Canakis AM, Cutz E, Manson D, O'Brodovich H (2002) Pulmonary interstitial glycogenosis: a new variant of neonatal interstitial lung disease. Am J Respir Crit Care Med 165(11):1557–1565

D'Aco K, Underhill L, Rangachari L et al (2012) Diagnosis and treatment trends in mucopolysaccharidosis I: findings from the MPS I registry. Eur J Pediatr 171(6):911–919

Deterding RR (2010) Infants and young children with children's interstitial lung disease. Pediatric Allergy Immunol Pulmonol 23(1):25–31

Deutsch GH, Young LR (2009) Histologic resolution of pulmonary interstitial glycogenosis. Pediatr Dev Pathol 12(6):475–480

Hendriksz CJ, Harmatz P, Beck M et al (2013) Review of clinical presentation and diagnosis of mucopolysaccharidosis IVA. Mol Genet Metab 110(1–2):54–64

Kiely BT, Kohler JL, Coletti HY, Poe MD, Escolar ML (2017) Early disease progression of Hurler syndrome. Orphanet J Rare Dis 12 (1):32

Kurland G, Deterding RR, Hagood JS et al (2013) 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 188(3):376–394

Moore D, Connock MJ, Wraith E, Lavery C (2008) The prevalence of and survival in mucopolysaccharidosis I: Hurler, Hurler-Scheie and Scheie syndromes in the UK. Orphanet J Rare Dis 3:24

Muenzer J, Wraith JE, Clarke LA, International Consensus Panel on Management and Treatment of Mucopolysaccharidosis I (2009) Mucopolysaccharidosis I: management and treatment guidelines. Pediatrics 123(1):19–29

Pizzutillo PD, Osterkamp JA, Scott CI Jr, Lee MS (1989) Atlantoaxial instability in mucopolysaccharidosis type VII. J Pediatr Orthop 9 (1):76–78

Poe MD, Chagnon SL, Escolar ML (2014) Early treatment is associated with improved cognition in Hurler syndrome. Ann Neurol 76(5):747–753

Smets K, Van Daele S (2011) Neonatal pulmonary interstitial glycogenosis in a patient with Hunter syndrome. Eur J Pediatr 170(8):1083–1084

Valayannopoulos V, de Blic J, Mahlaoui N et al (2010) Laronidase for cardiopulmonary disease in Hurler syndrome 12 years after bone marrow transplantation. Pediatrics 126(5):e1242–e1247

Wambach JA, Wegner DJ, Depass K et al (2012) Single ABCA3 mutations increase risk for neonatal respiratory distress syndrome. Pediatrics 130(6):e1575–e1582

Wraith JE, Clarke LA, Beck M et al (2004) Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). J Pediatr 144 (5):581–588