Pulmonary Manifestations of Endocrine and Metabolic Diseases in Children

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KEYWORDS

• Restrictive lung disease • Obstructive lung disease • Inborn errors of metabolism
• Endocrinological disorders

KEY POINTS

- The improved phenotyping of inborn errors of metabolism and endocrinopathies is increasingly revealing the extent of the pulmonary involvement in these systemic disorders.
- Early recognition can enable potential disease modifying therapy to be initiated and prevent needless investigation.
- Although particular diseases may predominately manifest as restrictive or obstructive lung disease, often a combination of both exist.

INTRODUCTION

Advances in technology, methodology, and deep phenotyping are increasingly driving the understanding of the pathologic basis of disease. The resultant improvements in patient identification and treatment are in turn impacting survival and unmasking new aspects of disease. This is especially true in endocrinology and inborn errors of metabolism, where disease-modifying therapies continue to be developed. Inherent to this evolving picture is the increasing awareness of the respiratory manifestations of these rare diseases. This review updates clinicians on these manifestations, stratifying diseases principally spirometerically; short sections on pulmonary hypertension and diseases with a predisposition to recurrent pulmonary infection are also included.

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This division is, however, artificial with many diseases having multiple pathologic effects on respiration. Owing to considerations of space, this review does not cover the impact of obesity.

OBSTRUCTIVE DISEASE

The endocrine and metabolic causes of obstructive airway disease are principally owing to alterations of the upper airways, typically presenting as either stridor or snoring with or without obstructive sleep apnea (OSA). The clinical hallmarks of these diseases and the approach to their diagnosis is detailed in **Table 1**. Acute stridor is a feature of some B vitamin deficiencies. In biotinidase deficiency, a recycling defect of biotin (vitamin B_7), a laryngeal spasm unresponsive to steroids but responsive within hours to oral biotin supplementation, can occur.[1–3] Stridor is also a feature of Brown–Vialetto–Van Leadre (BVVL), a disorder of gastrointestinal riboflavin (vitamin B_2) uptake, owing to defects in the luminal B_2 transporters RFTVT2 or RFTVT3. Although the classical clinical triad suggestive of BVVL is sensorineural deafness, bulbar palsy and respiratory compromise caused by muscular weakness,[4,5] it is now recognized that up to 50% of patients with BVVL presenting before the age of 3 years do so with stridor. Stridor has also been seen in a closely linked disorder, multiple acyl-coenzyme A dehydrogenase deficiency. Here the proteins, electron transfer flavoprotein, and electron transfer flavoprotein ubiquinone oxidoreducatase for which riboflavin is a precursor, accept the electrons generated by the flavin adenine dinucleotide–linked dehydrogenases. Abnormalities in either protein will ultimately also cause inhibition of the same fatty acid dehydrogenases as affected by BVVL. Unlike in BVVL, only severe multiple acyl-coenzyme A dehydrogenase deficiency has been linked with recurrent stridor,[6] with it not seeming to occur in milder multiple acyl-coenzyme A dehydrogenase deficiency variants.[7] Acute laryngospasm is also a symptom of hypocalcemia, whose main cause is hypoparathyroidism,[8] which in just under 10% of cases has a genetic basis.[9] Although this condition can be isolated or part of as syndrome, most typically the 22q11 microdeletion responsible for DiGeorge syndrome, it has also be seen to be secondary to defects in mitochondrial energetics such as Kearns–Sayre, MELAS [Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes], and mitochondrial trifunctional protein deficiency.[10–12]

However, the majority of endocrine and metabolic upper airway problems result from progressive anatomic changes. The archetypical examples are the lysosomal storage disorders, where inherited deficiencies in the activity of the inherent catabolic enzymes result in excessive substrate accumulation, which in turn trigger localized and systemic inflammatory responses. This response is most prominently seen in the mucopolysaccharidoses, a group of inherited conditions of glycosaminoglycan (GAG) degradation.[13] However, given their multilevel airway disease, they are considered in their own section in this article. Other lysosomal disorders resulting in upper airway distortion include the non/minimally neurologically affected patients with Faber disease. They generally suffer from progressive joint deformation and contractures, subcutaneous nodules, and inflammatory granuloma formation,[14] the latter occurring anywhere in the respiratory tract[15] and potentially causing extensive upper airway obstruction.[16] The respiratory hallmarks are a hoarse voice and respiratory insufficiency secondary to obstruction or interstitial pneumonitis. The pneumonitis of itself leads to death in the third or fourth decade of life. The upper airway lesions have been successfully surgically resected, but these lesions can reoccur.[16]

Soft tissue changes, especially tongue enlargement, is a feature of hypothyroidism, although alteration in central respiratory drive, suppression of the hypercapnic

Table 1
Causes of obstructive lung disease

Disease	Main Presenting Features	Investigation
Biotindase	Insidious onset of lethargy hypotonia, seizures after 7 wk. Hearing loss, marked dermatitis, optic atrophy, developmental delay	Urine organic acids Acylcarnitines Biotindase red cell assay
Brown–Vialetto–Van– Leare	Progressive pontocerebellar palsy and deafness. RFTV2 often also have sensory ataxia followed by distal weakness with or without nystagmus RFVT3—normally PC in infancy with hypotonia Both types→ rapidly progressive bulbar palsy and respiratory failure	Urine organic acids Acylcarnitines genetics
Hypocalcemia syndromic: 1. DeGeorge type 1 + 2 2. CHARGE 3. Autoimmune polyendocrine syndrome type 1 4. Hypoparathyroidism, sensorineural deafness and renal disease (hdr) 5) Kenney–Caffey syndrome type 1 + 2 6. Snajad–Sakati syndrome 7. Gracile bone dysplasia Mitochondrial: 1. MELAS 2. Kearns–Sayre 3. Mitochondrial trifunctional protein Autosomal dominant hypocalcemia: Autosomal dominant hypocalcemia type 1 Autosomal dominant hypocalcemia type 2 Isolated hypoparathyroidism	Congenital heart defects, thymic hypoplasia, cleft palate, parathyroid hypoplasia, developmental delay, renal, laryngotracheoesophageal and skeletal abnormalities Coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies Addison disease, hypoparathyroidism, and chronic mucocutaneous candidiasis Hypoparathyroidism, sensorineural deafness, renal dysplasia and occasional female genitourinary dysplasia Dwarfism, developmental delay (NB normal type 2) cortical thickening and medullary stenosis of long bones Intrauterine growth restriction at birth, microcephaly, congenital hypoparathyroidism, facial dysmorphism, mild intellectual delay Perinatally lethal condition, gracile bones with thin diaphyses, premature closure of basal cranial sutures, and microphthalmia Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, but multisystem disease	Genetic analysis of following genes, except where stated: DNA methylation MPLA CHD7 variants AIRE HDR TBCE/FAM111A TBCE FAM111A Mitochondrial DNA analysis: Most commonly mt point mutations 3243A-G, 8993T-G Mitochondrial DNA analysis: Acylcarntitines, HADHA HADHB gene analysis CASR/GNA11 GCM2/PTH/SOX3

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Table 1
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Disease	Main Presenting Features	Investigation
	Progressive external ophthalmoplegia, pigmentary retinopathy, and onset before 20 y of age, plus at least one of the followings: heart block, cerebellar symptoms, or cerebral spinal fluid protein levels of >100 mg/dL. Neonatal/early onset hypotonia, cardiomyopathy, liver dysfunction, hypoketotic hypoglycemia. 50% of patients have mild or asymptomatic hypocalcemia; about 50% have paresthesias, carpopedal spasm, and seizures; about 10% have hypercalciuria with nephrocalcinosis or kidney stones; >35% have ectopic and basal ganglia calcifications	
Farber disease	Triad of subcutaneous nodules, arthritis, and laryngeal involvement Hepatosplenomegaly	Acid ceramidase levels ASAH1
Prader–Willi syndrome	Neonatal hypotonia, facial dysmorphism with bifrontal narrowing then philtrum and almond shaped palpebral fissures, poor suck leading to failure to thrive, decreased responsiveness, small gentiles → subsequent hyperphagia developmental delay and short stature.	Genetic first line DNA methylation-specific MLPA

response,[17] and diaphragmatic weakness[18] also contribute to the multiple causes of respiratory dysfunction. A meta-analysis suggested that up to 30% of patients with overt clinical hypothyroidism have OSA,[19] but the historical link with pleural effusions is debated.[19] It is to be noted that obstruction has also been noted to occur in neonatal autoimmune hyperthyroidism owing to thyromegaly.[20]

Although the association of acromegaly and OSA is well established in adults,[21] there is little evidence that it causes problems in childhood. However the relationship of growth hormone supplementation in Prader–Willi syndrome (PWS) (see **Table 1**) and sudden death has been questioned.[20] Classically, the respiratory problems in PWS include OSA, central sleep apnea, and hypoventilation. Sudden death in patients with PWS has been long recognized and largely attributed to acute respiratory illness in combination with these preexisting respiratory problems. Although the body mass index standard deviation score has been found to correlate with OSA in children with PWS, the PWS-related obesity alone does not explain the association with OSA. Comparison studies of polysomnography (PSG) with non-PWS obesity-matched controls

showed that the PWS group had a significantly longer time with suboptimal oxyhemoglobin concentrations.[22] Poor upper airway tone, pharyngeal narrowing, micrognathia, adenoid hyperplasia, and decreased respiratory muscle strength all contribute, alongside an abnormal response to hypoxia and hypercapnia thought to be a result of hypothalamic dysfunction. Growth hormone deficiency is common in PWS, with an incidence of 40% to 100% reported. It is likely to contribute to the lower muscle mass, increased adipose tissue, and short stature found in PWS. In November 2000, growth hormone therapy was licensed in the UK for the indication "improvement of body composition and growth."[23] Growth hormone therapy is proposed to lead to adenotonsillar hyperplasia, which may lead to worsening OSA. Metabolic demand increases while on growth hormone therapy,[23] causing increased oxygen demand and leading to a relative state of hypoventilation. A preexisting decrease in hydration can be reversed while on GHT; this state may lead to a temporary increase in volume load and could also cause airway edema. All of these factors could contribute toward sudden death, especially in the context of an acute respiratory illness.

RESTRICTIVE DISEASE

The metabolic and endocrine causes of restrictive lung disease are principally caused by interstitial lung disease and musculoskeletal disease (**Table 2**).

Interstitial Disease

Many metabolic disorders can also manifest as interstitial lung disease. Indeed the European Childhood interstitial lung disease[24] and American[24] classifications have long recognized the potential for lysosomal storage disorders especially the sphingolipidoses to cause disease. However, it is becoming increasingly evident that, in addition to the lysosomal diseases identified, defects in other cellular biochemical pathways, such as amino acid transport and aminoacylation, can also result in diffuse chronic interstitial involvement.

The major pathologic mechanism underlying most metabolic causes of interstitial lung disease seems to be abnormal alveolar macrophage function. The presence of high concentrations lipid laden macrophages,[25] in the bronchoalveolar lavages of sphingolipid metabolic disorders such as Gaucher,[26,27] Niemann–Pick A, B, and C,[28] and animal models of lysosomal acid lipase[29] is extensively documented. In these disorders, it is the glycolipid accumulation within the macrophages and resultant interruption of normal intracellular vesicular cycling that result in the damaging proinflammatory cascades.[30–32] A number of disorders—that is Niemann–Pick A, B, and C, lysinuric protein intolerance, and methionyl tRNA synthetase, may also give rise to pulmonary alveolar proteinosis. In lysinuric protein intolerance, the alteration in intracellular arginine concentration is thought to impair macrophage Toll-like receptor function with resultant imbalance of proinflammatory and anti-inflammatory cytokines.[33] The mechanisms in methionyl tRNA synthetase are less well-defined, but global translational repression is thought to lead to the macrophage inflammatory response.[34]

Studies in lysinuric protein intolerance have shown infiltrative lung disease in approximately 2/two-thirds of patients when examined with high-resolution computed tomography (CT) scans.[35,36] However, a great degree of variability in respiratory presentation exists, even within families carrying the same mutation.[35] Thus, although patients can present with acute respiratory failure (16[37] to 60%[35]), some can be apparently clinically asymptomatic despite chronic radiologic changes.[36] There is extremely limited data on the efficacy of treatment, although the use of intravenous

Table 2
Causes of restrictive lung disease

Disease	Is Primary Presentation Pulmonary?	Main Presenting Features	Pulmonary Alveolar Proteinosis Seen	Investigation
NPA/B	Rarely	Common features: hepatosplenomegaly, growth restriction. and delayed bone age Raised triglycerides, low cholesterol Type A will typically have hypotonia and neurologic regression from 6 mo	Yes	Urine—oligosaccharides Blood—oxysterols white cell enzymology
Infantile-onset lysosomal acid lipase	No	Worsening gastrointestinal function then liver impairment <3 mo→ death 6–12 mo Increasing hemophagocytic lymphohistiocytosis phenotype on investigation with worsening disease	Yes	Blood—oxysterols White cell enzymology
Niemann–Pick C	No	1. Neonatal liver disease 2. Incidental splenomegaly 3. Progressive neurologic ataxia/vertical gaze palsy/ seizures and eventual neuroregression	Yes	Blood—oxysterols + chitotriosidase = suggestive Fibroblast—Phillipin staining Genetics
Lysinuric protein intolerance	No	Acute hyperammonemia Chronic—failure to thrive, protein intolerance, renal insufficiency, developmental delay, occasional hepatosplenomegaly and pancytopenia	Yes	Urine/plasma amino acid ratio Blood—ammonia (can be normal)
Methionyl tRNA synthetase	Yes	Multiorgan involvement with liver dysfunction prominent, occasional lactic acidosis and hyperammonemia	Yes	Genetics
MPS 1	Yes, but mainly obstructive	Coarse facies, otitis media, hepatosplenomegaly, umbilical/inguinal hernias, dysostosis multiplex, cervical spine instability potential neurologic decline (Hurler), corneal clouding, joint stiffness, valvular heart disease. Recurrent upper airway symptoms- infections, rhinorrhea, snoring	No	Urine—MPS screen Blood—white cell enzymology

MPS 2	Yes, but mainly obstructive	As in MPS1, but no corneal clouding	No	Urine—MPS screen Blood—white cell enzymology
Gaucher	No	Common features hepatosplenomegaly, anemia, thrombocytopenia, acute painful crisis, failure to thrive, horizontal saccade initiation failure with progression to more severe oculomotor apraxia	No	White cell enzymology
HPP	No	Perinatal from foreshortened/limb deformation, caput memebanecum, osteogenic spurs in midshaft, period apnea ulnas, fibula skeletal hyopmineralization on radiographs Infantile—Pc before 6 mo, poor feeding, failure to thrive, hypotonia, rickets, with or without increased intracranial pressure, blue sclera, vitamin B_6-dependant epilepsy, hypercalcemia and hypercalciuria Childhood PC >6 mo premature deciduous tooth loss, rachiatic deformities of wrists, costocondrial junction and genu varus/valgum, skeletal pain and delayed walking. Marrow edema mimicking osteomyelitis, craniosynostosis, characteristic radiology	No	Liver function –alkaline phosphatase Genetics ALPL
OI		Type 1—non deforming autosomal dominant, blue sclera Type 2- severe perinatal lethal autosomal recessive Type 3- severe progressive deformity autosomal recessive Type 4-moderate severity autosomal dominant normal sclera Type 5-calcification of interosseous membranes $\pm$ hypertrophic callus NB hearing loss, dental involvement/joint hypermobility, increased cardiac valvular disease variable dependent on severity	No	80%–85% COL1A1 or COL1A2

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Table 2
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Disease	Is Primary Presentation Pulmonary?	Main Presenting Features	Pulmonary Alveolar Proteinosis Seen	Investigation
Infantile-onset Pompe disease	Possible respiratory distress	Typically Pc <6 mo with respiratory distress, cardiomegaly, developmental delay, hypotonia, poor feeding and weight gain	No	White cell enzymology, urinary Glc4,
Phosphomannomutase-2 deficiency—CDG	No	Neonatal hypotonia, inverted nipples and unusual subcutaneous fat pads, ataxia, mental retardation apparent from later childhood while muscular atrophy and hypogonadism is seen in later life	No	Transferrin isoelctrofocusing

corticosteroids and whole lung lavages in established respiratory failure, was thought to be ineffective in the French cohort.[35] There is a single recorded heart–lung transplant[38] in a 3-year-old child with acute respiratory failure unresponsive to intravenous corticosteroids and lavage.

In methionyl tRNA synthetase, a number of case series have emphasized its impact on the lungs.[39,40] The largest of these was a retrospective cohort of 29 patients the median age of onset of respiratory symptoms was 2.5 months (range, 0.5–72.0 months), with 26 patients presenting before 1 year of age. Fibrosis was present in 19 of 28 patients (69%) who underwent lung biopsy.[41] An initial CT scan was available for 17 patients (median age, 10 months) and showed intralobular septal thickening (100%), ground glass opacities (94%), and consolidation (76%). In the 13 patients who had a repeat CT scan (median age, 10 years), the consolidation had resolved although in 12 signs of fibrosis were present. The restrictive pattern on pulmonary function testing mirrored this, whereas 15 of the 18 had a diffusing capacity of the lung for carbon monoxide of less than 80% of the predicted value.[41] Twenty-six patients were treated with lavages, 14 with steroids, and 1 underwent transplantation, with the latter showing no recurrence of pulmonary alveolar proteinosis 1 year after the transplant. There was no overall correlation between outcome and any of the treatment modalities. Twelve of the 29 patients died, the majority before 3 years of age; survivors were aged between 1.1 and 24.9 years.

The sphingolipid disorders have varying degrees of lung involvement being near universal in Niemann–Pick B, where the leading causes of death are respiratory and liver failure.[42] Ninety percent of a prospective series of 54 pediatric and adult patients had parenchymal changes on radiographs, which increased to 98% on CT scan.[43] The CT scans showed ground-glass opacities, interlobular septal thickening, and intralobular lines, mainly in the lower zones.[43] These changes, although not pathognomonic,[44] are, in the context of Niemann–Pick B, highly suggestive of pulmonary alveolar proteinosis. Cysts, thought to be secondary to air trapping[45] and even emphysematous changes,[46] have been described, but are rare.

Niemann–Pick C, a defect in lysosomal egress of unesterified cholesterol lipids,[47] tends to have a milder respiratory phenotype. Although overall 95% of cases are caused by defects in the NPC1 gene, those documented with severe lung manifestations have typically had defects in the NPC2 gene.[48–50] These cases typically develop respiratory failure within the first year of life,[49] with ground glass changes on chest radiographs and pulmonary alveolar proteinosis on autopsy.[50]

In the third of the sphingolipidoses, Gaucher's disease, pulmonary and overall severity have been correlated.[51] Patients have traditionally been divided into 3 major subgroups depending on the absence (type I) or presence (type II and III) of neurologic symptoms.[52] Although generally having milder visceral disease, the majority of enzyme replacement therapy (ERT)-naive type I patients still had abnormalities in pulmonary function, particularly a decrease in functional residual capacity and diffusing capacity of the lung for carbon monoxide, which preceded radiologic changes.[53] In the pre-ERT era, even patients with type I Gaucher could develop respiratory failure secondary to alveolar occlusion by Gaucher cells, most typically in splenectomized patients.[27,54] Autopsy findings also demonstrated Gaucher's cell invasion of the septal capillaries, fitting with reports of pulmonary hypertension.[55] Although ERT has decreased the degree of lung involvement even in those type 1 patients with severe initial disease,[56,57] in older patients, respiratory response may be minimal.[51] Respiratory complications, although similar in the chronic neuropathic form (type III) tend to be more prevalent[58] and also include pulmonary haemorrhage.[59] Although lavage[60] and even intrabronchial ERT have been tried, the combination of ERT and substrate

reduction may be the best therapy for improving pulmonary function.[61] Lung transplantation has been successfully undertaken both in the pediatric and adult populations.[25,62]

Although pulmonary involvement has been seen in Wolmans disease, historically these patients presented with growth failure and liver dysfunction within the 1st months of life and typically died of ensuing liver failure by 4 months.[63] With the advent of ERT the respiratory complications have become more overt. These patients suffer from an interstitial lung disease,[64] which may not be surprising given the disruption in surfactant production seen in animal models.[65]

Within mucopolysaccharidosis (MPS), interstitial disease is predominately seen in neonates, before commencement of ERT, with both MPS1 (Hurler syndrome)[66] and MPS II (Hunter syndrome).[67] These patients all showed glycogen deposition on lung biopsy, leading to an initial misdiagnosis of pulmonary interstitial glycogenosis. However, interstitial lung disease has also been seen in patients who should, theoretically, have been provided with adequate replacement enzyme.[68,69] Although in both the lung disease was postulated to be multifactorial, the former responded to increased enzyme provision, whereas the latter responded to steroids after spinal surgery.

Although type 2 diabetes has been seen of itself, even when weight gain has been accounted for, to be a risk factor for restrictive lung disease in adults,[70] comparable studies in pediatrics have not yet been performed.

Musculoskeletal Causes

Although potentially all causes of impaired respiratory muscle function can cause a degree of restrictive lung disease, it is beyond the capacities of this review to expand on the multiple genetic defects that decrease the mitochondrial energy production interfering with either respiratory drive or muscle function. We concentrate on 3 disorders that typify this form of restriction.

Infantile-onset Pompe disease is an autosomal recessive lysosomal storage disorder is caused by a deficiency of the enzyme acid α-glucosidase.[71] The resulting accumulation of glycogen in lysosomes triggers inflammatory pathologic cascades[72] that principally affect skeletal and cardiac muscles. Patients typically present within the first few months of life, with a combination of cardiorespiratory insufficiency, hypotonia, and failure to thrive.[73,74] Untreated patients follow a rapid, progressive, and ultimately fatal course, dying typically between 7 and 9 months of age from cardiorespiratory failure.[73] The advent of ERT has markedly changed the overall survival; however, data from the UK and Germany suggest that ventilator-free survival was at best 40% in those treated on standard doses, because respiratory muscle failure still results in insufficiency in the majority of patients.[75,76]

Hypophosphatasia (HPP) is a rare disorder of bone mineralization caused by mutation in the *ALPL* gene, which codes for tissue-nonspecific alkaline phosphatase. Mineralization of the tissues is controlled by inhibitor of mineralization, inorganic pyrophosphate, which is deactivated by alkaline phosphatase dephosphorylation. In HPP, a low alkaline phosphatase concentration causes undermineralization of the skeleton and severe rickets. HPP is a heterogenous disorder with the most severe form, perinatal HPP, presenting with severe hypomineralization of the fetal skeleton; the moderately severe form, infantile HPP, presents within 6 months of age. Infants with perinatal and infantile HPP manifest with varying degree of respiratory failure secondary to undermineralized thoracic cage, hypoplastic lungs and hypotonia requiring respiratory support. Until recently, perinatal HPP was fatal with 100% mortality.[77] ERT with asfotase alfa significantly improves survival compared with historic controls and this result is secondary to improved mineralization of the thoracic skeleton, allowing these

infants to survive with respiratory support.[78] Requirements for respiratory support are variable, with some children requiring it until 4 years of age.[79] A multidisciplinary team consisting of an intensivist, pulmonologist, physical rehabilitation therapist, and metabolic bone disease specialist is required for the management of neonates and infants with HPP manifesting with respiratory complications.[80] If prolonged respiratory support is predicted, a tracheostomy should be considered, and long-term home ventilation should be planned. Tracheobronchomalacia can complicate ventilatory requirements and duration and, therefore, if clinically indicated, tracheobronchoscopy should be performed.

Osteogenesis imperfecta (OI) refers to a group of disorders where abnormalities in collagen formation and/or deposition result in defective bone matrix formation. Most common forms of OI, types I to IV, are caused by autosomal dominant mutations in the *COL1A1* and *COL1A2* genes coding for type 1 collagen. The nosology of OI has, however, expanded, with multiple genes now identified which can cause autosomal dominant and autosomal recessive OIs.[81] OI clinically manifests with frequent nontraumatic fractures; whereas moderate to severe OI presents with limb deformities, thoracic deformities from rib and vertebral fractures, and hypoplastic lungs. Indeed, the most common cause of death is secondary to pulmonary diseases,[82] which may in part reflect the abundance of type 1 collagen in the connective tissues surrounding the alveoli structures. The risk of pulmonary disease is directly related to the severity of OI; neonates with severe OI (type III and autosomal recessive) may develop respiratory failure requiring ventilatory support from chest wall deformities and pulmonary hypoplasia.[83] In addition, kyphoscoliosis from vertebral collapses and rib deformities, pectus carinatum, decreased diaphragmatic movement (abdominal contents pressing on diaphragm), airway distortions, and restrictive pulmonary abnormalities can in combination significantly decrease alveolar ventilation.[84] Furthermore, ineffective clearance of secretion and infections can lead to bronchiectasis. Finally, soft skull and platybasia can cause basilar invagination that, in severe cases, may disturb respiratory function secondary to brain stem compression and hydrocephalus. There are reports of ventilatory requirements for this complication.[85] Although there is no specific disease-modifying therapy for OI type IV, bisphosphonates have been shown to prevent vertebral fractures, decrease the frequency of rib fractures, and prevent worsening of chest deformities, therefore contributing to improving respiratory function. Physical rehabilitation assists in positioning and effective clearance of secretions. Some children may require spinal surgeries for the correction of kyphoscoliosis, which also contributes to improving respiratory function. Yearly monitoring with lung function testing, imaging, and pulse oximetry can help in screening for respiratory complications.[84] In those infants with severe OI requiring ventilatory support, a global view must be taken because they normally also have developmental delay, neurologic complications, and multiple fractures, and are completely dependent on care givers. Therefore, the ethics of treatment, especially long-term ventilation, should be considered carefully, and palliative care should be offered after a discussion with the family.

It is to be noted that dysostosis multiplex like skeletal changes have been seen in the congenital disorders of glycosylation (CDGs).[86] These are a rapidly evolving field of disorders where defects in the normal post-translational glycosylation processes occurring in the endoplasmic reticulum and Golgi complex result in aberrant tertiary protein structure. By far the best described is phosphomannomutase-2 deficiency, which has been seen to have very similar thoracic changes to those described in the MPSs. This multisystem disease presents normally in infancy with hypotonia, inverted nipples, and unusual subcutaneous fat pads. However, patients often

develop ataxia–mental retardation in childhood and muscular atrophy and hypogonadism in later life.[87] Diagnosis of the CDGs has been based on the glycosylation pattern of transferrin with differing glycosylation patterns occurring in differing groups of CDGs with these patterns being recognized using electrophoretic analysis. It is to be noted that this transferrin isoelectofocusing can give false-negative results in the first 3 months of life.[87]

Other causes of restrictive lung disease include disorders of thyroid transcription factor TITF1/NKX2.1, which is required for pulmonary development, with affected infants suffering from pulmonary hypoplasia.[88]

MIXED AIRWAY DISEASE

Mucopolysaccharidosis

Inherited defects in the catabolic pathways of the GAGs heparan, dermatan, and keratan sulfate have all been associated with obstructive symptoms.[13,89] At a cellular level, substrate accumulation results in a localized proinflammatory response.[90,91] Although the major impact of heparan sulfate is seen on neurologic tissue,[92] it is the accumulation of dermatan[93,94] and keratan moieties[95] that have the greatest effect on extracellular matrix structure and airway growth and caliber.

The impact of MPS on airway function can be seen from the fact that, despite the advances in diagnostics and therapeutics, respiratory disease remains the leading cause of morbidity and mortality in MPS and is also the most prominent cause of patient-perceived impaired quality of life.[96] Airway obstruction can occur in both the upper and lower airways in MPSs.[13,97,98] The principle cause of the obstruction in MPS I, II, VI, and VII is the multilevel GAG deposition, which in the upper airway leads to nasal mucosal hypertrophy, macroglossia, and adenotonsillar hypertrophy.[99–101] Registry data show that 80% of patients with MPS I demonstrate OSA before the age of 2 years.[102] Despite disease-modifying therapies such as ERT and bone marrow transplantation, 84% of patients with MPS I still undergo adenotonsillectomy.[102] GAG deposition can also result in enlarged and redundant supraglottic tissues, especially in MPS II, where prolapse into the laryngeal inlet can result in severe compromise.[103,104]

Although GAG accumulation leads to overt narrowing of the upper airways, this hypertrophy is often compounded by local inflammation and weakness resulting in laryngopharyngeal malacic changes as well as subglottic laryngotracheomalacia.[105,106] This combination of GAG accumulation and malacial changes leads to multilevel airway obstruction.[107] With the exception of patients with MPS III, these intrinsic upper airway changes are further complicated by limited mouth opening.[107] The impairment of mouth opening is secondary to a combination of temporomandibular joint dysfunction[108] and/or overgrowth of the mandibular coronoid processes.[109]

GAG deposition and inflammation also occur in the lower airway,[110–112] with airway narrowing resulting from malacia seen in all the MPS subtypes.[106,113,114] However, the most severe tracheal abnormalities are seen in MPS IV (tortuosity and “buckling”).[115] This exaggerated response is thought to be due to abnormal cartilage metabolism and imbalances between the relatively normal longitudinal growth of the trachea and the severely restricted thoracic cage growth. Indeed, in MPS IV, the tracheal narrowing has been documented as early as 2 years of age. Although the study was cross-sectional, all patients over 15 years of age had a decrease of at least 50% in tracheal caliber, suggesting progression with age.[115]

The combination of chest wall deformities and hepatosplenomegaly[115] does make a significant contribution to the respiratory impact of the MPSs (**Table 3**). Chest wall deformities are part of the general dysostosis multiplex seen in MPS. Particularly the

Table 3
The respiratory impact of the mucopolysaccharidoses

MPS	Name and Enzyme Defect	Main GAGs on Urine Screening	Clinical Symptoms	Respiratory Manifestations		
				Upper Airway	Lower Airway	Restrictive Disease
I	Hurler (H) Hurler-Scheie (HS) Scheie (S) Iduronidase deficiency	DS HS	Coarse facies, otitis media, hepatosplenomegaly, umbilical/ inguinal hernias, dysostosis multiplex, cervical spine instability potential neurologic decline (Hurler), corneal clouding, joint stiffness, valvular heart disease	+++	++	++
II	Hunter Iduronate—I-sulphatase deficiency	DS HS	As MPS1 but no corneal clouding	+++	++	+
II	Sanfilippo (A–D) A) Heparan *N*-sulfatase B) Alpha-N-acetylglucosaminidase C) Acetyl-coenzyme A:alpha-glucosaminide acetyltransferase D) *N*-acetylglucosamine-6-sulfate	HS	Stage 1—Initially asymptomatic/mild developmental delay Stage 2—hyperactivity and grossly impaired sleep (mainly neurologic) Stage 3—neurologic decline gastrostomy and bed bound	–/+ Otitis media common	–/+	–/+
III	Morquio (A and B) A) *N*-acetylgalactosamine 6-sulfatase B) Beta-galactosidase	KS, CS	Severe skeletal deformity cervical spine instability genu valgum, pectus carinatum and kyphoscoliosis? short stature, valvular heart disease, corneal clouding, joint hypermobility	++	+++	+++
VI	Maroteaux–Lamy *N*-acetylgalactosamine 4-sulfatase	DS, CS	As per MPS 1, but with a greater chance of cervical spine instability but without/ minimal neurologic compromise	+++	++	++
VII	Sly Beta-glucuronidase	DS, HS, CS	Hydrops fetalis and as per MPS I	++	++	++

pectus carinatum, kyphoscoliosis and rib abnormalities—both shape (oar) and angulation (more horizontal)—as well as induration of the costovertebral complex and the elevation of the diaphragms all contribute to the reduction in pulmonary function.[13,115] Chest wall pathology is most closely tied to stature and is thus most prevalent in MPS IV, although it is also seen in the more severe phenotypes of MPS I, II, and VI.[13] Finally, MPS I, IV, and VI are associated with atlantoaxial subluxation and odontoid hypoplasia that may result in spinal cord compression[116] that, if involving the C3 to C5 nerve roots, can decrease diaphragmatic function and ventilation.[13]

A comprehensive evaluation of respiratory function should be attempted in all patients with MPS, with spirometry, PSG, flexible nasoendoscopy, and imaging all contributing to overall management and perioperative safety.[107,117] Although central apnoeas have been noted with progressive neurologic involvement,[117] the commonest form of sleep disordered breathing found on PSG is OSA. The limited published PSG data suggest that OSA is present in 70% to 100% of patients with MPS I, II, and VI, although most prominently in MPS I and II.[118–121] Although nasoendoscopy is a very useful tool to access laryngeal involvement and inspiratory supraglottic collapse, this tool can be challenging in the young and those with neurocognitive impairment.[122] Three-dimensional CT reconstructions of the large airways can help with preoperative planning, with reported alterations in anesthetic decision making in more than 20% of cases.[105]

Disease Associated with Recurrent Respiratory Infections

A number of both endocrine and metabolic disorders are associated with increased risk of respiratory infections. The best example is the autosomal recessive form of pseudohypoaldosteronism owing to defective action of the epithelial sodium channel, whose 3 subunits are encoded by SCNN1A, SCNN1B, and SCNN1G. Alpha subunit variants have been associated chronic disease and are reportedly clinically indistinguishable from cystic fibrosis.[123,124] Impaired neutrophil function in GSD 1B and G6PC3 (severe congenital neutropenia type 4) also predispose to increased respiratory infections. Recurrent infection is also a hallmark of immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome and immune dysregulation, polyendocrinopathy, enteropathy, X-linked–like disorders, with up to 30% of affected patients having recurrent pulmonary disease.[125] The most significant metabolic impairment of the immunologic function, however, is seen in patients with adenosine deaminase 1, which in its most severe form causes severe combined immunodeficiency. The recurrent opportunistic infections that arise from decreased T and B cells result from the build-up of adenosine and its derivatives.[126] By the time of diagnosis, these patients often have chronic respiratory insufficiency and autoimmune phenomena, including cytopenias and antithyroid antibodies. Allergies and an elevated serum IgE are often present.[127]

PULMONARY HYPERTENSION

Although in the World Health Organization classification of pulmonary hypertension, metabolic disease falls within category 5, the multifactorial subclassification,[128] the commonest metabolic causes are due to mitochondrial dysfunction. It is seen in both defects predominately affecting mitochondrial energetics such as LIPT1,[129] Tmem70,[130] and NFU1,[131] and in those affecting more diverse mitochondrial functions such as the glycine cleavage system (nonketotic hyperglycinemia),[132] DNA transcription (mitochondrial seryl-tRNA synthetase),[133] or amino acid transport (SLC25A26).[134]

Typically, the disorders predominately affecting energetics present in the neonatal period, are multisystemic in nature and have a prominent neurologic component.

Outside the neonatal period, metabolic disorders resulting in pulmonary hypertension are rare. Historically, Gaucher's disease was the commonest cause with pulmonary hypertension occurring in 5% of splenectomized patients.[54,135] However, the advent of ERT and the resultant reduction in splenectomies, seems to have resolved this.

Intracellular processing defects in cobalamin (vitamin B_{12}), typically cobalamin C has been seen to present with isolated pulmonary hypertension in both children[136] and adults.[137] It has, however, recently also been associated with diffuse lung parenchymal disease.[138] It seems most likely that the microangiopathy associated with the high levels of homocysteine and organic acids is the basis of the pulmonary hypertension. The typical presentation of cobalamin C is with developmental delay and failure to thrive from poor enteral tolerance in the first 6 months of life.[139]

CLINICAL CARE POINTS

- The normal range of biochemical investigations especially those used in the investigation of biochemical disease are not as well established as more classical normal ranges and more prone to sampling errors. Thus, if is there is disparity between the clinical and biochemical phenotype further discussion with the reference laboratory should be sought.
- While next generation sequencing is revolutionising medicine, given the number of VUS (variants of unknown significance) generated in panel testing, functional investigation where possible as outlined above is still the authors first line suggestion currently.

DISCLOSURE

The authors have nothing to disclose.

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