Pulmonary Involvement in Adult Patients with Inborn Errors of Metabolism

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Keywords

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Abstract

Inborn errors of metabolism (IEM) are rare individually, but taken together, they affect 1 in 1,000 people. Most of the disease becomes apparent at the pediatric age; however, with the identification of late-onset forms, and with improved survival, several of these conditions may be found in adults of all ages. While the lung is not typically a primary site of clinical disease in patients with IEM, in some of them it can be a significantly affected organ with associated severe respiratory complications. Lung involvement can be a late-onset feature of a complex multisystemic disease, but sometimes it can also be the only manifestation of underlying IEM. The aim of this review is to focus on specific IEM associated with lung disease in adults and to provide the reader with an overview of the diagnostic workup, overall disease management, and specific treatments for the respiratory manifestations. Clinical suspicion, early recognition, prompt diagnosis, and appropriate care of the respiratory manifestation are crucial, as they can affect both the life expectancy and the quality of life of these patients.

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Introduction

Inborn errors of metabolism (IEM) result from the absence or abnormality of an enzyme leading to the accumulation or deficiency of a specific metabolite in various organs. Approximately 500 human diseases due to IEM are currently recognized. This number is increasing as novel techniques become available and allow the identification of new biochemical and molecular abnormalities [1]. IEM are rare individually, but taken together, they affect about 1 in 1,000 people [2]. In most cases, the disease becomes apparent at the pediatric age; however, with the identification of late-onset forms, and with improved survival, several of these conditions may be found in adults of all ages. Although metabolic specialists with expertise in the field of IEM are present in large academic centers, primary care physicians are typically the first to see these patients [3].

From a pathophysiological perspective, IEM can be divided into the following 3 categories (Table 1):

- 1 Disorders involving complex molecules: this group involves cellular organelles and includes diseases that alter the synthesis or catabolism of complex molecules. All lysosomal storage disorders (LSD), peroxisomal disorders, and congenital disorders of glycosylation and of cholesterol synthesis belong to this group.

Table 1. Characteristics of inborn errors of metabolism in adults with pulmonary manifestations

Group of disorders and subtype	Enzyme deficiency	Gene	OMIM #	Clinical features	Respiratory manifestations	FU investigations	Treatment
<i>Disorders involving complex molecules</i>							
NP-B	ASM deficiency	<i>SMPD1</i>	257200	(Hepato)splenomegaly, normal intelligence, growth restriction	ILD, “crazy paving” on HRCT	CXR HRCT PFT	Supportive ± BAL ERT (phase II trial)
NP-C	Impaired cholesterol esterification	<i>NPC1</i> and 2	252220	Variable age at onset, hepatosplenomegaly, neurological involvement	ILD, pulmonary alveolar proteinosis	CXR HRCT PFT	Supportive SRT
Gaucher disease type 1	β-Glucocerebrosidase	<i>GBA</i>	230800	Visceral (splenomegaly), hematological and skeletal symptoms	ILD, lobar consolidation, PAH	HRCT PFT Cardiac US	ERT SRT PAH treatment
Gaucher disease type 3	β-Glucocerebrosidase	<i>GBA</i>	231000	Same as type 1; brainstem dysfunction, neurodegenerative	Same as type 1	Same as type 1	Same as type 1
Fabry disease	α-Galactosidase A	<i>GLA</i>	301500	Cardiomyopathy, renal failure, stroke, hearing loss	Fixed airway obstruction	PFT Cardiac US	ERT Supportive
LOPD	Acid α-glucosidase	<i>GAA</i>	232300	Slowly progressive weakness	RF	PFT SNIP/MEP	ERT Ventilatory support
Mucopolysaccharidoses	Lysosomal enzymes in the GAG breakdown pathway	*	*	Connective tissue changes, skeletal deformities, hepatomegaly ± psychomotor retardation	Airway obstruction, restrictive disease, OSA	PFT, polysomnography	ERT (MPS I, II, and VI) HSCT (MPS I)
<i>Disorders that give rise to intoxication</i>							
LPI	Reabsorption defect of the dibasic amino acids	<i>SLC7A7</i>	222700	Osteoporosis, renal failure, hemolysis, gastrointestinal symptoms	Alveolar proteinosis, pulmonary fibrosis	CXR HRCT	Low-protein diet, citrulline supplementation ± BAL
<i>Disorders involving energy metabolism</i>							
Mitochondrial diseases	RC defect	Nuclear, maternal genes	n.a.	Muscle, CNS, multisystem diseases	RF, OSA, PAH	HRCT PFT	Antioxidants ± CPAP

ASM, acid sphingomyelinase; BAL, bronchoalveolar lavage; CNS, central nervous system; CPAP, continuous positive airway pressure; CXR, chest X-ray; ERT, enzyme replacement therapy; FU, follow-up; GAG, glycosaminoglycan; HRCT, high-resolution computed tomography; HSCT, hematopoietic stem cell transplantation; ILD, interstitial lung disease; LPOD, late-onset Pompe disease; LPI, lysinuric protein intolerance; MEP, maximal expiratory pressure; MPS, mucopolysaccharidosis; n.a., not applicable; NP-B, Niemann-Pick disease type B; NP-C, Niemann-Pick disease type C; OSA, obstructive sleep apnea; PAH, pulmonary arterial hypertension; PFT, pulmonary function test; RC, respiratory chain; RF, respiratory failure; SNIP, sniff nasal inspiratory pressure; SRT, substrate reduction therapy; US, ultrasound. * Genes and OMIM # for mucopolysaccharidoses in adults: MPS I: IDUA/252800; MPS II: IDS/309900; MPS IIIA: SGSH/252900; MPS IIIB: NAGLU/252920; MPS IIIC: HGSNAT/252930; MPS IIID: GNS/252940; MPS IVA: GALNS/253000; MPS VI: ARSB/253200; MPS VII: GUSB/253200; MPS IX: HYAL1/601492.

- Disorders of small molecules that give rise to intoxication: this group includes inborn errors of intermediary metabolism (e.g., most organic acidurias, urea cycle disorders, sugar intolerance, and metal intoxication) that lead to an acute or progressive intoxication from the accumulation of toxic compounds proximal to the metabolic block.
- Disorders primarily affecting energy metabolism: this group consists of IEM with symptoms due mainly to a deficiency in energy production and includes mito-

chondrial disorders, disorders of glycolysis, glycogen metabolism, creatine metabolism, fatty acid oxidation, and ketone metabolism.

While the lung is not typically a primary site of clinical disease in patients with IEM, in some of them it can be a significantly affected organ with associated severe respiratory complications [4–6]. Lung involvement can be a late-onset feature of a complex multisystemic disease, but sometimes it can also be the only manifestation of underlying IEM.

Fig. 1. Chest high-resolution computed tomography images of a 51-year-old male patient with Niemann-Pick disease type B. In the upper lung zones, a subtle thickening of alveolar septa is visible (**a**). In the middle (**b**) and lower lung zones (**c**), widespread ground-glass opacities with locally superimposed septal thickening and small regions of spared parenchyma produce a “crazy paving” pattern.

The aim of this review is to focus on specific IEM associated with lung disease in adults and to provide the reader with an overview of the diagnostic workup, overall disease management, and specific treatments for the respiratory manifestations.

Disorders Involving Complex Molecules

Most IEM associated with lung disease belong to the group of disorders involving complex molecules, and more specifically LSD. Lysosomes are required for the intracellular breakdown of various biological molecules such as glycolipids, oligosaccharides, and glycoproteins.

Defective lysosomal enzymes cause the accumulation of those substrates within the organelle and progressive functional impairment of the affected system. Symptoms vary depending on where in the body the storage occurs, although characteristics of many lysosomal disorders include coarsening of facial features, hepatosplenomegaly, bone disease, and/or neurologic impairment. Subgroups of LSD with respiratory impairment consist of sphingolipidoses and mucopolysaccharidoses (MPS).

Sphingolipidoses

Niemann-Pick Disease

Niemann-Pick disease type A (NP-A) and type B (NP-B) are caused by autosomal recessive disorders which

Fig. 2. Foamy macrophage histology image of a 51-year-old male patient with Niemann-Pick disease type B.

result from deficient activity of acid sphingomyelinase (ASM), a lysosomal enzyme encoded by the *SMPD1* gene [7]. NP-A is characterized by a severe neurodegenerative disease of infancy and by early death, usually in the first 3 years of life, while NP-B has a later onset and a milder manifestation than NP-A and most patients survive to adulthood. The primary storage material in NP-B is sphingomyelin, a major structural component of cells. From a clinical perspective, any adult patient presenting with splenomegaly and dyspnea should be investigated for NP-B. Impairment ranges from asymptomatic to severe respiratory failure with complete oxygen dependence [8–10]. Nearly all adult patients have interstitial lung disease. In later life, progressive pulmonary infiltration tends to be the cause of major morbidity and mortality [11].

The pathophysiology of pulmonary disease involves the accumulation of lipid-laden macrophages in the alveolar spaces and septa, bronchial walls, and pleura, resulting in progressive restriction of lung volumes and impaired gas exchange [12]. On chest radiography and high-resolution computed tomography (HRCT), patients show diffuse reticular interstitial infiltrates. The linear and ground-glass opacities intermittently overlap in a manner that is classically described as “crazy paving” [13] (Fig. 1). Most individuals have progressive gas exchange abnormalities, although the extent of the radiographic findings may not correlate with impairment of pulmonary function [14]. Histologically, alveoli with vacuolated foamy macrophages (Fig. 2), called “sea-blue histiocytes”

due to the blue May-Giemsa staining, are typically found [15, 16].

The diagnosis is based on reduced ASM activity in isolated leukocytes and/or cultured fibroblasts and identification of disease-causing mutations in the *SMPD1* gene. Treatment of NP-B is mainly supportive. Patients with symptomatic restrictive lung disease should be managed with ventilator support as required. Whole lung lavage has been shown to be useful in isolate cases with severe pulmonary disease [17]. Enzyme replacement therapy (ERT) is currently under investigation: the olipudase alfa study is a phase II/III, randomized, multicenter study recently initiated to evaluate the efficacy and safety of recombinant human ASM in patients with NP-B. Phase I, performed on 5 patients, showed promising results, as gas exchange and interstitial lung disease were improved after 26 weeks of treatment [18]. Therefore, close monitoring of such patients using routine HRCT and pulmonary function testing is recommended in order to identify those who might benefit from supportive treatment until further therapy becomes available.

NP-C is a different disorder based on impairment of intracellular lipid transport and consecutive accumulation of unesterified cholesterol and glycosphingolipids (GSL) in the brain and other tissues. The first neurological symptoms typically occur within the second or third decade of life in most patients, but onsets after 50 years of age have also been reported [19]. NP-C is diagnosed by biochemical tests showing impaired cholesterol esterification and positive Filipin staining in cultured fibroblasts, and more recently by the finding of an abnormal pattern of cholesterol oxidation products (oxysterols) in blood [20]. Ninety-five percent of the patients have mutations in the *NPC1* gene, and the remaining patients have mutations in the *NPC2* gene. Patients presenting with the disease as adults typically do not have pronounced pulmonary involvement. Pulmonary alveolar proteinosis (PAP) may occur due to loss of normal NPC2 protein expression in alveolar macrophages and accumulation of cholesterol-rich surfactants [21]. Oral administration of a substrate reduction therapy (miglustat), an imino sugar that reduces the intracellular storage of glucosylceramide, seems to be successful in preventing dysphagia and airway aspiration by slowing or stopping the neurological progression of the disease [22, 23].

Gaucher Disease

Gaucher disease (GD) is an autosomal recessive disorder resulting from deficient glucocerebrosidase activity, a lysosomal enzyme encoded by the *GBA* gene. The pri-

mary metabolic defect resides in blocking lysosomal degradation of glucosylceramides, which accumulate as lipid-laden macrophages (Gaucher cells) in the liver, spleen, bone marrow, central nervous system, and lung [24].

Three clinical phenotypes are recognized (type 1, non-neuronopathic form; type 2, acute neuronopathic form; type 3, chronic neuronopathic form), which can all present with lung involvement. Adult patients essentially present with type 1 or 3. Pulmonary manifestations are more likely to occur as a late complication, following splenectomy [25, 26], likely as a consequence of a shift of storage macrophages from the spleen to the lungs. The following can be observed: interstitial lung disease, alveolar/lobar consolidation, and pulmonary hypertension caused by the storage of lipid-laden macrophages in the interstitium, bronchi, alveoli, or pulmonary vasculature. Pulmonary hypertension seems to be related in most cases to preexisting interstitial lung disease, usually in patients with severe GD [27]. Hepatosplenomegaly progressively leads to small lung volumes with secondary hypoventilation due to limited diaphragmatic excursion. Patients who are homozygous for the c.1448T>C (p.Leu444Pro) mutation [28] have a higher risk of interstitial lung disease, which suggests a genotype-“respiratory” phenotype correlation.

HRCT demonstrates interlobular septal and intralobular interstitial thickening, irregular interfaces at the pleural surfaces, and a ground-glass appearance, corresponding to both the alveolar and the interstitial components of pulmonary involvement [29]. Histologically, Gaucher cells within the alveoli have a large cytoplasmic mass with a striated appearance that has been linked to a “wrinkled tissue paper” appearance. The diagnosis of GD relies on demonstration of deficient glucocerebrosidase enzyme activity in isolated leukocytes and identification of disease-causing mutations in the *GBA* gene. Bone marrow biopsy may reveal typical Gaucher cells. In addition, there is an increase in chitotriosidase enzyme activity, which is a sensitive marker of macrophage storage used to monitor treated patients.

Two different types of treatment are available: (1) ERT with recombinant human glucocerebrosidase or (2) substrate reduction therapy with miglustat. Type 1 GD patients respond well to ERT [30] with improvement of hepatosplenomegaly and hematological parameters as well as increased well-being [31]. Nevertheless, there is a wide heterogeneity in the response of pulmonary manifestations to ERT [30]. Schiffmann et al. [32] reported that miglustat in combination with ERT may have positive effects by improving pulmonary function.

Fabry Disease

Fabry disease (FD) is an X-linked disorder caused by a deficiency in activity of the lysosomal enzyme α -galactosidase A, resulting in the progressive accumulation of neutral GSL in various cells and tissues, mainly podocytes, cardiomyocytes, and vascular cells (smooth muscle cells and endothelial cells) [1]. The intracellular GSL storage and vascular remodeling result in cellular dysfunction and decreased organ perfusion, triggering inflammation, fibrosis, and organ damage and eventually leading to premature death [33].

Most male patients (hemizygotes) affected by the classic form of the disease (residual enzymatic activity <1%) remain clinically asymptomatic during the earliest years of life. However, during childhood and/or adolescence, they develop angiokeratomas, acroparesthesia, hypo-/anhidrosis, nonspecific digestive disorders, microalbuminuria, and chronic fatigue [34]. In adulthood, the progression of organ damage is responsible for chronic/end-stage renal disease as well as life-threatening cardiovascular and cerebrovascular complications. Heterozygous women often exhibit a later onset of findings and milder symptoms than males. However, their presentations may range from asymptomatic to a severe phenotype similar to the classic form observed in hemizygous males, due to skewed X-inactivation [35]. Men affected with the non-classic form of the disease (residual enzymatic activity between 1 and 30%) are usually mildly or nonsymptomatic during childhood and adolescence, but they develop isolated hypertrophic cardiomyopathy in later adulthood [36]. The diagnostic criteria for FD differ according to sex and phenotype [34]. ERT for FD has been available since 2001 [37, 38].

Involvement of the lungs appears both in hemizygous and in heterozygous patients around the fourth decade, concomitantly with kidney, heart, and nervous system complications [39]. By electron microscopy, GSL deposits have been observed mainly in bronchial (smooth muscle cells and bronchial ciliated epithelial cells) and vascular pulmonary cells [40, 41]. Moreover, lung biopsies also revealed peribronchiolar fibrosis and bronchial smooth muscle cell hyperplasia. Affected patients typically exhibit dyspnea, wheezing, and dry cough in the absence of simultaneous severe cardiac problems [39, 42].

In a recent review, Franzen et al. [43] analyzed 13 publications (a total of 299 patients) addressing pulmonary involvement in FD. Based on the current literature, obstructive lung disease, defined by forced expiratory volume in 1 s/forced vital capacity (FEV₁/FVC) <70%, was up to 10 times more frequent (32.2 vs. 3.4%) in the FD

population as compared to a healthy control population matched for gender, age, and smoking status. Also, the prevalence of obstructive ventilatory defects in the FD population was comparatively higher than the prevalence of chronic pulmonary obstructive disease in the general population [44]. Acute reversibility testing with short-acting bronchodilators usually does not lead to any significant improvement in FEV₁ [45].

The severity of the bronchial obstruction is dependent on male gender and age. However, some female patients seem to be as severely affected as male patients – only 10 years later, which is in line with the involvement of other organs in heterozygous patients. Data concerning the severity of airway obstruction and smoking history are conflicting [39, 43]. The mechanism of small-to-medium airway disease in FD is probably secondary to hyperplasia of the bronchiolar/bronchial smooth muscle cells, leading to a fixed narrowing of the airways partly due to a defect of smooth muscle cell relaxation [40]. The lung interstitium may be affected at later stages of pulmonary involvement [39]. Pulmonary function testing should be proposed before ERT initiation, and in patients over 30 years of age. The efficacy of ERT and/or long-acting bronchodilators and/or inhaled corticosteroids on bronchial involvement has not yet been sufficiently evaluated in FD. In all cases, smoking cessation should be encouraged.

Glycogen Storage Diseases

Late-Onset Pompe Disease

Late-onset Pompe disease (LOPD), also known as glycogen storage disease type II glycogenosis, is an autosomal recessive disorder based on reduced enzyme activity of lysosomal acid α -glucosidase. The accumulation of glycogen in skeletal and respiratory muscles can result in myopathy, with progressive deterioration in both mobility and pulmonary function. Adult patients generally present with the late-onset form, which can occur at any age starting from childhood, with slow muscular involvement of the trunk and proximal limb muscles, absence of cardiac involvement, and a less severe outcome than with the classic form.

In over 70% of LOPD patients, respiratory failure is the most common cause of mortality [46]. In some cases of LOPD, respiratory failure may precede the onset of limb muscle weakness [47]. The pulmonary dysfunction in LOPD patients is related to weakness of the diaphragm and the accessory respiratory muscles with subsequent peripheral alveolar hypoventilation and daytime hypercapnia [48, 49]. The development of respiratory insufficiency requires the initiation of ventilatory support. The

occurrence of progressive, sometimes fatal, respiratory failure is primarily due to the inability of the respiratory muscles to generate normal levels of pressure during inspiration and expiration [50, 51].

Since 2006, ERT with recombinant human α -glucosidase has represented the only available treatment with proven efficacy in improving or stabilizing motor and respiratory function in at least two-thirds of LOPD patients as well as in reducing the need for ventilator support [52]. However, pulmonary function might progressively deteriorate even in treated patients, likely because ERT has been started late after the occurrence of irreversible muscle damage [53]. The effect of ERT on respiratory function seems related to the patient's age and residual pulmonary function at baseline. Therefore, early recognition of respiratory manifestations is crucial to achieve optimal therapeutic benefits for individuals with LOPD. Evaluation of respiratory involvement is based on standard pulmonary function tests, including FVC in the sitting and the supine position with measurement of the volume drop between the upright and the supine position (FVC drop), which has been suggested as a marker of diaphragmatic dysfunction [54, 55].

Mucopolysaccharidoses

MPS are caused by a deficiency of the lysosomal enzymes needed for the glycosaminoglycan (GAG) breakdown pathway. There are 8 different types of MPS, each caused by a deficiency in 1 of 10 different enzymes involved in the degradation of GAG. Inheritance is autosomal recessive, except for MPS type II, which is X-linked. All MPS disorders are progressive, multivisceral diseases involving the musculoskeletal system (bones and joints), heart, lungs, eyes (cornea, retina, and optic nerves), liver, and spleen, and, in some of the diseases, the central nervous system [56].

Respiratory manifestations are very common in patients with MPS and are often a predominant symptom [57]. Mechanisms that predispose MPS patients to respiratory failure include airway obstruction and restrictive disease. Airway obstruction is due to both GAG deposition in the upper airways (which are increasingly narrowed) and skull, spine, and trachea deformities. Restrictive disease is caused by GAG deposition in the pulmonary interstitium, by chest deformities, and by impaired diaphragmatic motility. Clinical manifestations include dyspnea, impaired sputum clearance, cough, and wheezing. Upper airway obstruction with obstructive sleep apnea (OSA) combined with chest deformity and tracheal distortion due to spinal deformity leads to frequent total

airway collapse, as reported in adults with Morquio syndrome (Fig. 3). GAG deposition in the pharynx, larynx, and trachea may increase the anesthetic risk and require dedicated airway management.

Patients should be managed by anesthesiologists familiar with MPS. All patients should receive regular vaccination for pneumococcus and influenza, early treatment of respiratory tract infections, and manual and/or mechanical techniques for sputum clearance [57]. Current management guidelines for MPS I and MPS VI therefore recommend pulmonary function testing at diagnosis and every 6–12 months thereafter [58]. Polysomnography should be performed on all patients at diagnosis and during follow-up for early detection of OSA. ERT used for patients with MPS I, II, and VI has proven to have a beneficial effect on pulmonary function [59–61]. The improvement in adult patients is attributed to multiple mechanisms, such as reduced GAG accumulation in the airways, improvement in mobility, shrinking of the liver and spleen, and increased chest wall compliance, respiratory muscle strength, and diaphragmatic excursion [61–64]. Hematopoietic stem cell transplantation (HSCT) is the recommended treatment for severely affected, young MPS I patients, and has proven to prevent cognitive decline due to the permeability of the blood-brain barrier to stem cells. The effect of HSCT on other MPS types tends to be poor [65], and its effect on pulmonary function is only based on case reports, some suggesting a positive impact on snoring and OSA [66].

Disorders of Small Molecules That Give Rise to Intoxication

Respiratory symptoms are often the first, nonspecific sign of acute metabolic decompensation in this group of disorders. Both in infants and in adults, tachypnea occurs as a physiological response to metabolic acidosis. Hyperventilation is also the main sign of hyperammonemia, even in the absence of metabolic acidosis, as ammonia is a central stimulator of ventilation, often leading to secondary respiratory alkalosis [67]. Therefore, in aminoacidopathies (such as maple syrup urine disease), in organic aciduria (such as methylmalonic or propionic aciduria), and in urea cycle disorders (such as ornithine transcarbamylase deficiency), tachypnea may be the presenting symptom, usually in the absence of other signs of pneumopathy. In these cases, tachypnea is usually not isolated, but associated with signs of encephalopathy.

Fig. 3. Chest high-resolution computed tomography images with sagittal (a) and frontal (b) reconstructions of a 24-year-old woman with mucopolysaccharidosis type IV (Morquio syndrome). The abnormal position and shape of the sternum is seen in the sagittal plane (a). Tracheal deformity and stenosis is visible in the frontal plane (b).

Although primary lung involvement is restricted to the disorders discussed below, it is important for primary care physicians to be aware of the acute respiratory signs of IEM, since they allow early management of life-threatening decompensations.

Disorders of Amino Acid Metabolism

Lysinuric Protein Intolerance

Lysinuric protein intolerance (LPI) is an inherited hyperdibasic aminoaciduria caused by defective cationic

Fig. 4. Chest high-resolution computed tomography image of a 28-year-old woman with lysinuric protein intolerance. Diffuse ground-glass opacities are present. Multiple small cysts are visible in the subpleural regions and are scattered throughout the lung parenchyma. Source: Courtesy of Prof. Vincent Cottin, Reference Centre for Rare Pulmonary Diseases, Lyon University Hospital, Lyon, France.

amino acid transport, exerted by the γ -L system, at the basolateral membrane of epithelial cells in the intestine and kidney. LPI is an autosomal recessive disease caused by mutations in the *SLC7A7* gene, which encodes for the γ -LAT-1 protein.

The diagnosis of LPI relies on clinical and biochemical findings [68]. Most clinical manifestations of LPI in infancy include gastrointestinal disease, poor growth, early osteoporosis, renal disease, and aversion to protein-rich food. Biochemically, patients present with defective reabsorption of dibasic amino acids (lysine, arginine, and ornithine), which are elevated in urine and decreased to borderline low levels in plasma. Treatment with a low-protein diet supplemented with citrulline provides clinical improvement, mainly reducing hyperammonemia [69].

Respiratory involvement is commonly seen in LPI and may develop through 3 stages. In the first stage, interstitial opacities are visible on chest X-ray in asymptomatic patients. In the second stage, diffuse reticulonodular interstitial densities appear. Progression to respiratory insufficiency and PAP represents the third stage of the disease. PAP is characterized by the accumulation of foamy macrophages filled with a lipoproteinaceous material within the alveoli [70]. Fatal respiratory insufficiency was mainly described in patients below 15 years of age [71, 72]. Genotype is not correlated with phenotype, as family relatives carrying the same mutation may present with completely different pulmonary involvements [73]. Bilat-

eral infiltrates are typically present on chest radiography, and HRCT reveals ground-glass opacities and airspace consolidation with interlobular septal thickening, resulting in the characteristic diffuse or localized “crazy paving” pattern. In a Finnish series, most adult patients had interstitial lung disease visible on HRCT, while only a few developed clinical symptoms [72]. It could be that interstitial lung disease lacks the characteristic feature of “crazy paving” on HRCT (Fig. 4) [74]. Therefore, in the presence of unexplained lung involvement in a young subject, it is essential to consider screening for LPI.

The pathogenesis of pulmonary disease in LPI remains obscure. The mechanisms leading to fibrosis may be secondary to or associated with those causing alveolar proteinosis. The impaired clearance of apoptotic cells in LPI, causing alveolar proteinosis, may lead to development of aberrant inflammatory and immune responses and, consequently, fibrosis. It has also been suggested that increased synthesis of nitric oxide in the presence of inflammatory cytokines may result in progressive lung disease [69]. Treatment with arginine is a matter of debate, as it might worsen the outcome of LPI by increasing NO production. Low-dose citrulline supplementation is recommended, since citrulline is converted to arginine. Unfortunately, early treatment with citrulline supplementation seems to have no effect on respiratory complications [75]. High-dose oral corticosteroids may slow down the progression of lung disease if started early, but it might not be effective in all cases and remains controversial [76]. Whole lung lavage does not appear to be consistently effective in eliminating the lipoproteinaceous material from the alveolar spaces [72]. Lung transplantation is not recommended, due to possible recurrence of the disease in the transplanted lungs [77]. HSCT has been discussed as a possible treatment for PAP in LPI. The rationale of this therapeutic approach would rely on the hypothesis of a defective function of lung macrophages [75, 78].

Disorders Involving Energy Metabolism

Mitochondrial Diseases

Mitochondrial diseases are a group of disorders caused by dysfunction of the mitochondrial respiratory chain. They present with a wide range of multisystemic clinical signs [79]. Although neuromuscular impairment is a common manifestation, mitochondrial disorders can also affect other organ systems, either exclusively or in combination. Pulmonary manifestations associated with mitochondrial diseases include respiratory failure, re-

current sleep apnea, structural abnormalities of the diaphragm, and pulmonary hypertension. Respiratory failure may occur owing to muscle fatigue, either in the setting of exercise intolerance associated with lactic acidosis or from hypoventilation induced by events such as pneumonia. Recurrent sleep apnea has been noted in association with encephalopathy, being mostly central in origin. Pulmonary hypertension has been reported in pediatric case reports [80] and could be explained by the fact that mitochondria play essential physiological roles in the pulmonary vasculature through oxygen sensing and the production of reactive oxygen species [81]. Diagnosis of mitochondrial diseases requires a multifaceted approach, including biochemical, histopathological, and electron microscopic examination, enzymatic assays of different tissues, and molecular analysis [82]. As a clinical pitfall, the lungs are never the only organ involved, since usually those tissues requiring high-energy consumption (renal tubular cells; liver, muscle, and heart myocytes; brain cells) are mostly affected.

The mainstay of current treatment for patients with mitochondrial diseases is supportive. Exercise appears to be beneficial in mitochondrial disorders. Aerobic exercise has been associated with increased peak work and oxidative capacity and decreased exercise intolerance [83]. There is no proven effective therapy for the primary mitochondrial disorders, although many agents are being evaluated in clinical trials. Pharmacologic strategies that have been tested for these conditions include the use of respiratory chain cofactors, treatment with antioxidants, and agents that correct secondary biochemical defects. The impact of those pharmacologic treatments on pulmonary function remains unknown [84]. Adult patients with previously undiagnosed IEM rarely present with respiratory symptoms as the initial manifestation. However, there are several case reports of adults presenting, even at old age, with respiratory failure due to a previously undiagnosed mitochondrial myopathy [85].

In case of pulmonary involvement, pulmonary function tests should be performed at baseline, and again as

clinically indicated when symptoms occur. Interventions include noninvasive measures such as continuous positive air pressure. Some patients with chronic respiratory failure and repetitive intubation may require specific anesthetic management such as tracheotomy [86].

Conclusion

The number of adult patients with an IEM is increasing due to improved clinical care and extended diagnostic modalities. The respiratory system is frequently involved in those patients and warrants attention in terms of specific management and monitoring. The largest group consists of those with interstitial lung disease due to storage of complex molecules, such as sphingolipidosis. Upper airway disease is common in MPS – specifically MPS I, II, IV, and VI – and respiratory failure with decreased FVC can be a prominent symptom of LOPD. Management should be discussed in a multidisciplinary team including a pulmonologist and a metabolic physician, and ideally supported by physicians with special skills in the management of airway disease, such as anesthesiologists and ear, nose, and throat specialists. In the past, the management of several IEM was limited to supportive therapy and symptom relief. Nowadays, different therapeutic approaches are available, including ERT, HSCT, and substrate reduction therapy, which improve the prognosis of respiratory diseases associated with IEM. Clinical suspicion, early recognition, prompt diagnosis, and appropriate care of the respiratory manifestation are crucial, as they can affect both the life expectancy and the quality of life of these patients.

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