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Interstitial lung disease in newborns

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A B S T R A C T

The term 'interstitial lung disease' (ILD) refers to a group of disorders involving both the airspaces and tissue compartments of the lung, and these disorders are more accurately termed diffuse lung diseases. Although rare, they are associated with significant morbidity and mortality, with the prognosis depending upon the specific diagnosis. The major categories of ILD in children that present in the neonatal period include developmental disorders, growth disorders, surfactant dysfunction disorders, and specific conditions of unknown etiology unique to infancy. Whereas lung histopathology has been the gold standard for the diagnosis of ILD, as many of the disorders have a genetic basis, non-invasive diagnosis is feasible, and characteristic clinical and imaging features may allow for specific diagnosis in some circumstances. The underlying mechanisms, clinical, imaging, and lung pathology features and outcomes of ILD presenting in newborns are reviewed with an emphasis on genetic mechanisms and diagnosis.

1. Introduction

Interstitial lung disease (ILD) is a heterogeneous group of rare disorders of diverse and often unknown etiologies that cause acute or chronic respiratory signs and findings. Whereas the term ILD has become broadly accepted as a result of the pathologic changes observed in the pulmonary interstitium, these disorders often involve the airspaces, and the term 'diffuse lung disease' (DLD) may be more accurate. ILD/DLD has generally been classified in adults based upon the underlying histopathology, but the disorders seen in adults differ from those seen in children and even more so in neonates, and thus different approaches are needed. In the past ten years, collaborative efforts between clinicians, imagers, and pathologists have led to a classification system more appropriate for infants and children. Whereas this approach was based largely upon lung pathology, it is being increasingly recognized that many of the disorders affecting newborns and young infants have a genetic basis, which may allow for a specific diagnosis through non-invasive means. Recent advances in genetics based upon next-generation sequencing methods have allowed for more cost-effective genetic testing panels for known disorders and identification of new disorders through agnostic approaches using whole-exome or whole-genome sequencing. The approach to the diagnosis of ILD and understanding of the specific disorders is thus likely to continue to evolve rapidly. This review focuses on those disorders that typically present in the newborn period and which are likely to result in hypoxemic respiratory failure.

2. Classification of childhood interstitial lung disease (chILD)

A classification of ILD specific for infants aged <2 years was developed based upon review of clinical, imaging and lung biopsy data [1]. More than half (57%) needed supplemental oxygen at birth, and 21% had biopsies performed before age 2 months. Subsequent studies have utilized and expanded on this classification scheme, with the majority of included subjects having needed supplemental oxygen or respiratory support at birth, and disorders likely to present in the neonatal period have consistently accounted for more than half of cases (Fig. 1) [2–5]. Estimates of the prevalence of ILD in children have ranged from 0.13 to 16 cases per 100,000 children per year [6], but the overall incidence of ILD in newborns is unknown. ILD/DLD in newborns is associated with significant mortality, and children who succumbed early in infancy may not have been included in estimates that focused on older children. With improved recognition and ability to diagnose these disorders, more accurate estimates of their incidence and prevalence are likely to emerge.

2.1. Diffuse developmental disorders

Disorders that interrupt lung development result in diffuse lung

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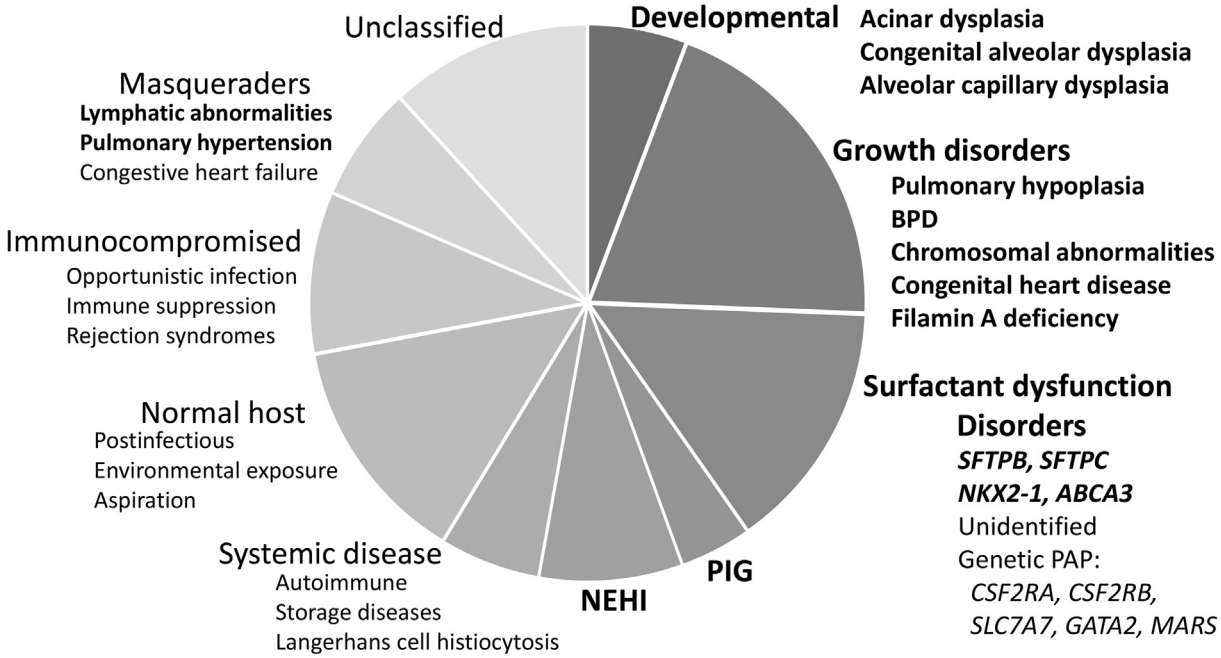

Fig. 1. Distribution of diagnoses of interstitial lung disease in infants aged <2 years. The chart indicates the percentage of cases in each diagnostic category collated from retrospective studies [1,3–5,35]. Disorders and diagnoses in bold type are those more likely to present in the newborn period. BPD, bronchopulmonary dysplasia; NEHI, neuroendocrine cell hyperplasia of infancy; PIG, pulmonary interstitial glycogenosis; PAP, pulmonary alveolar proteinosis.

disease in term newborns, characterized clinically by hypoxemic respiratory failure that is refractory to medical therapy. These conditions include acinar dysplasia, congenital alveolar dysplasia, and alveolar capillary dysplasia with misalignment of the pulmonary veins (ACDMPV) [3]. In acinar dysplasia (also referred to as type 0 congenital pulmonary airway malformation or CPAM), the pathology is consistent with an arrest of lung maturation at the pseudoglandular to canalicular phase of lung development, with no or few acinar structures and absent alveoli. These children are difficult to support even with maximal medical therapy and the diagnosis is usually made at autopsy. In congenital alveolar dysplasia the arrest of lung development is slightly later, at the late canalicular to saccular phase of lung development [3]. These infants also usually have severe lung disease and pulmonary hypertension but may be able to be supported and the diagnosis established by biopsy. There are few published studies on congenital alveolar dysplasia, which may overlap other lung developmental disorders, and no systematic evaluation of genetic causes has been performed. The incidence of developmental disorders is unknown. ACDMPV accounted for the majority of cases of irreversible lung dysplasia in one small series [7].

There are multiple reports of familial cases of acinar dysplasia strongly indicative of underlying genetic mechanisms, but no single candidate gene has been implicated. Isolated cases in association with other phenotypic findings have been associated with mutations in *FGFR2* and *TBX4* [8,9]. Pathologic features of acinar dysplasia were observed in children subsequently found to have *ABCA3* mutations, but other causative genes cannot be excluded [10,11].

2.2. Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV)

This is an increasingly recognized form of diffuse lung disease resulting from abnormal lung development. Affected infants generally present with severe hypoxemic respiratory failure and pulmonary hypertension shortly after birth that is refractory to maximal medical management, including extracorporeal membrane oxygenation, leading to death in the neonatal period. Whereas this presentation and course is still the most frequently observed, relatively milder forms of the disease and later presentation have been recognized. Affected children frequently (50–75%) have abnormalities in other organ systems, including congenital heart disease, gastrointestinal, and genitourinary malformations. Recognition of familial cases suggested a genetic basis for the disorder, and deletions of and mutations in the *FOXF1* gene, which encodes a transcription factor important in vascular development, have been identified in the majority of infants with ACDMPV [12,13].

In addition to DNA sequence variants that alter or disrupt the *FOXF1* coding sequence, deletions involving part or all of the gene have accounted for a substantial portion of cases. Many of these deletions are located in the 5′ untranslated region, which contains a lung-specific enhancer region and harbors two long non-coding RNAs (lncRNA) that are important for proper expression of the *FOXF1* gene; an additional enhancer is located in the intron [14,15]. This has important implications for diagnosis, as the absence of a mutation by sequence analysis does not exclude a deleterious *FOXF1* variant, and specifically designed or targeted microarray analysis may be needed to identify causative variants. As a *FOXF1* genetic variant cannot be identified in some infants with ACDMPV, other loci likely remain to be identified [15].

The majority of disease-causing *FOXF1* variants appear to be *de novo* and result in sporadic disease. However, well-documented familial cases indicate that there is variable expressivity of disease. This variability results from several mechanisms, including somatic mosaicism, and from the *FOXF1* locus being partially imprinted, such that manifestation of disease depends upon which parent transmitted the mutant allele and whether the mutation was in the coding region or involved deletion of the enhancer region [15–17].

Although rare, the diagnosis of ACDMPV should be suspected in a term infant with severe pulmonary hypertension of the newborn

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