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Review

Early onset children's interstitial lung diseases: Discrete entities or manifestations of pulmonary dysmaturity?

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Educational aims

The reader will come to:

1. Appreciate the spectrum of interstitial lung diseases presenting early in life related to abnormalities of lung development (NEHI, PIG, alveolar-capillary dysplasia spectrum).
2. Realise that these may not be specific entities, but there are overlap syndromes and associations with extrapulmonary abnormalities.
3. Understand that these histological patterns are the beginning not the end of the diagnostic journey, and should trigger a search for underlying in particular genetic abnormalities.

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ABSTRACT

Interstitial lung diseases in children (chILD) are rare and diverse. The current classifications include a group of early onset chILD specific to infancy, namely neuro-endocrine cell hyperplasia of infancy (NEHI), pulmonary interstitial glycogenosis (PIG) and the alveolar capillary–congenital acinar dysplasia (ACD–CAD) spectrum, as well as alveolar growth disorders. NEHI and PIG cells are seen in the normal developing foetal lung. We hypothesise that these conditions are in fact overlapping manifestations of pulmonary dysmaturity, respectively of airway, mesenchymal and vascular elements, rather than discrete clinical conditions in their own right. Clinically, these present as respiratory distress in early life. Mild cases rightly never undergo lung biopsy, and for these the clinical description 'persistent tachypnoea of infancy' has been proposed. In terms of pathology, we reviewed current literature, which showed that NEHI cells decline with age, and are not specific to NEHI, which we confirmed by unpublished re-analysis of a second dataset. Furthermore, specific genetic disorders which affect pulmonary maturation lead to a histological picture indistinguishable from NEHI. PIG and ACD–CAD are also associated with pulmonary growth disorders, and manifestations of PIG and NEHI may be present in the same child. We conclude that, contrary to current classifications, NEHI, PIG, and ACD–CAD should be considered as overlapping manifestations of pulmonary dysmaturation, frequently associated with disorders of alveolar growth, rather than as separate conditions. Identification of one of these patterns should be the start, not the end of the diagnostic journey, and underlying in particular genetic causes should be sought.

In a landmark report, Deutsch et al. [1] proposed a classification of children's interstitial lung disease (chILD) which included disorders of growth and development, and conditions specific to

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infancy, namely Neuroendocrine Cell Hyperplasia of Infancy (NEHI) and pulmonary interstitial glycogenosis (PIG). Subsequent classifications also accepted these two conditions as specific to infancy [2–4]. The term NEHI was initially applied to a group of infants with similar clinical findings (persistent tachypnoea) in whom the major histological finding was increased numbers of bombesin-positive neuroendocrine cells. Subsequently, diagnosis was on imaging findings alone, although these are not 100% specific. By contrast, PIG had a more diverse presentation but more specific histological appearances, namely the presence of interstitial glycogen positive cells. Neuroendocrine cells (NEC), are seen in the normal developing human foetal lung, where they are thought to induce proliferation of airway epithelial and mesenchymal cells as well as differentiation of alveolar type II cells [5–9] but, although aggregates of glycogen particles are present during lung development in type II cells [10–12], they are not normally found in post-partum pulmonary interstitial cells [10,13,14]. In combination with other signs of delayed alveolar maturation, the accumulation of glycogen in foetal mesenchymal cells has been thought to be a disease-reactive process [15]. The actual detailed roles of bombesin and glycogen positive cells in lung maturation are unclear, nor is it clear whether they contribute to the pathophysiology of chILD or are merely markers of another process.

The hypothesis underpinning this review is that NEHI and PIG are part of a spectrum of growth and developmental delay rather than discrete entities, and this spectrum is characterised by dysmaturation of one or more compartments of the foetal lung, namely the foetal airway (bombesin-positive cells), interstitium (glycogen positive cells), alveolar structure (relative lack of alveolar growth/hypoplasia) and the foetal pulmonary vasculature (persistent pulmonary hypertension of the newborn and the infantile overlap syndrome of idiopathic pulmonary hypertension; spectrum of congenital acinar dysplasia, alveolar capillary dysplasia and the less well characterised congenital alveolar dysplasia). We acknowledge that this hypothesis is controversial, and that the evidence is by no means clear. However we suggest that the Identification of one of these patterns should be the start, not the end of the diagnostic journey, and underlying in particular genetic causes should be sought.

NEHI: DYSMATURATION OF THE FOETAL AIRWAYS?

NEHI is a term which was coined to describe otherwise well infants with any or all of chronic tachypnoea, retractions, crackles and hypoxaemia; in lung biopsies haematoxylin and eosin (H&E) staining was essentially normal, but there was increased staining for the neuropeptide bombesin in the most distal airway cells [16–18]. If performed, infant pulmonary function tests show evidence of air trapping [18,19], and airflow obstruction persists into childhood [20]. High resolution CT (HRCT) appearances in infants with NEHI have been suggested to be diagnostic, obviating the need for lung biopsy in the appropriate clinical context [21,22]. Findings include well demarcated geographic ground glass opacities centrally and in the right middle lobe and lingula (Fig. 1). Although the specificity of HRCT for the diagnosis of NEHI was suggested to be 100% [22], similar HRCT findings can be found in infants with different biopsy proven ILD (Fig. 2).

However, new studies cast doubt on the existence of NEHI as a discrete clinical entity. Large numbers of data points for normal values of bombesin positive cells, and formal criteria for defining neuroendocrine cell excess are lacking [23]. NEHI cells were counted in 73 biopsies from children with a wide range of chILD [24]. There were seven cases of NEHI, who as expected, had increased NEHI cells and percentages of airways with NEHI cells. However bombesin positive cells were also seen in follicular bronchiolitis and surfactant protein disorders to a similar extent, and similar although less in PIG, non-specific interstitial pneumonia (NSIP) and children with infections and vascular disease presenting as chILD. Importantly, considering all biopsies together, the percentage of NEHI cells declined with age.

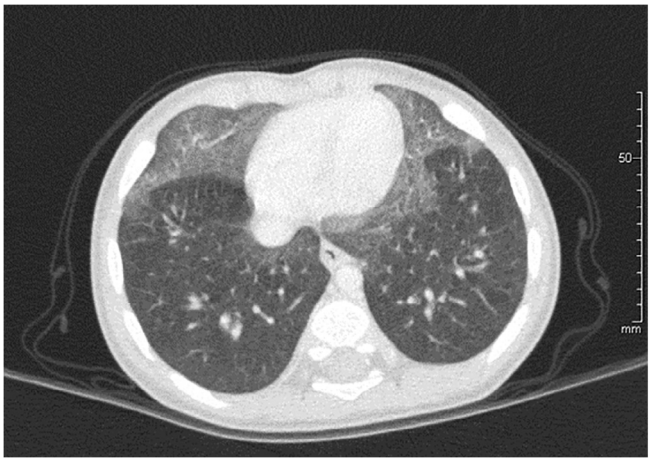

Fig. 1. Classical HRCT scan appearances of Neuroendocrine cell hyperplasia of infancy (NEHI).

Rauch et al. [25] studied 80 infants with clinically suspected interstitial lung disease, primarily ground glass changes on HRCT scanning and the exclusion of surfactant dysfunction disorders and cardiovascular causes. Cases with characteristic HRCT distribution of ground glass were called usual persistent tachypnoea of infancy (PTI), and those with atypical or minor other findings were called aberrant PTI. There was no difference in clinical outcomes between usual and aberrant PTI, and, in those who underwent a lung biopsy, there were more neuroendocrine cells in PTI than controls, with no differences between usual and aberrant PTI. There were four patients whose biopsies also met the criteria for PIG, three of whom also had increased bombesin positive cells. They confirmed that there was an age-dependency of the bombesin positive cell numbers and airways (Fig. 3).

Other reports challenge the existence of NEHI as a discrete entity. In an interesting kindred, five patients over two generations were heterozygous for a missense NKX2.1/TTF-1 mutation in codon 191 predicting the substitution of leucine for arginine in the homeodomain which is extensively evolutionary conserved [26,27]. They presented with respiratory distress and failure to thrive in infancy, with improvement over time. In those in whom these investigations were performed, HRCT and lung biopsy showed the typical appearances of NEHI. Given that NKX2.1/TTF-1 is a key regulator of multiple steps of lung development and maturation [28,29], we hypothesise that this mutation led to airway and alveolar developmental delay manifested by prominent persistent bombesin positive cells. Examining the published micrographs, there is possibly additional alveolar maturational delay, and indeed one adult patient had reduced carbon monoxide transfer at follow up, suggesting alveolar growth may not always have been normal. The alternative, that two rare diseases coincidentally co-existed in multiple members of this kindred (NEHI and a purely pulmonary form of 'brain-thyroid-lung' syndrome) is very unlikely, but cannot be excluded. Finally, the Forkhead box protein P-family (FOXP) is a transcription factor for normal airway branching and development [30–32]. Notably, patients with mutation of FOXP1 show exactly the same clinical course and HRCT scans as patients diagnosed with NEHI [33].

Taken together, these data argue that NEHI is not a discrete condition, but rather, that persisting neuroendocrine positive cells are

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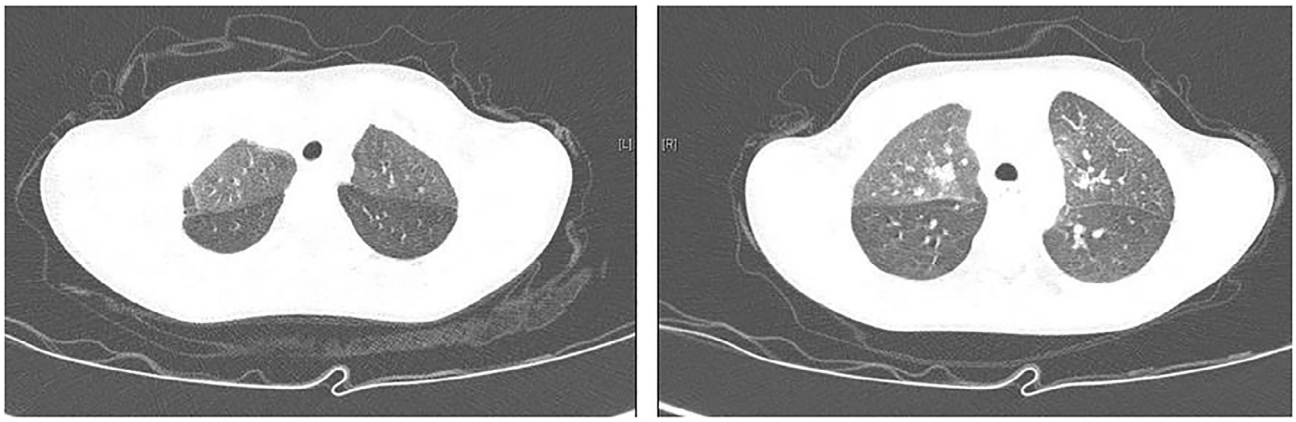

Fig. 2. Eighteen month old child with HRCT appearances which mimic neuroendocrine cell hyperplasia of infancy but in fact the underlying biopsy proven diagnosis was desquamative interstitial pneumonia. Whole exome sequencing of the surfactant protein genes revealed no mutations.

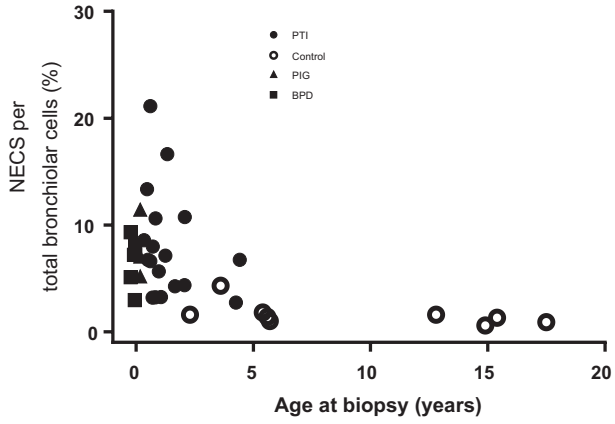

Fig. 3. Age dependency of neuroendocrine cells (NECs) expressed as indicated on the y-axis based on the numbers obtained in Rauch et al. 2016 [25].

a marker of airway dysmaturation, which may co-exist with other maturational lung defects. We suggest that PTI is best used as a clinical descriptor of these patients [25] if no biopsy is carried out; and it perfectly describes what is seen. If such patients are biopsied, and increased numbers of bombesin positive cells are seen, either isolated or with other abnormalities, this should be considered as evidence of 'dysmaturation of the fetal airway'. We hypothesise that unless and until specific quantitative criteria which distinguish NEHI from other chILD with distal airway bombesin positive cells can be stated, NEHI cannot be described as a distinct condition. The actual detailed roles of bombesin and glycogen positive cells in lung maturation are unclear, nor is it clear whether they contribute to the pathophysiology of chILD or are merely markers of another process entity.

DYSMATURATION OF THE FOETAL MESENCHYME (PIG)

PIG was first described [14] in seven infants who presented with tachypnoea, respiratory distress and non-specific pulmonary infiltrates in the first month of life. Light and electron microscopy confirmed the presence of glycogen granules within spindle shaped cells which expanded the interstitium. These cells were vimentin positive but negative for macrophage markers. There was no pathological extrapulmonary glycogen deposition. Six infants survived; the seventh died of the complications of bronchopulmonary dysplasia and extreme prematurity, but of note, three other children were born preterm, likely more than would be expected by chance. The authors reviewed over 1000 paediatric lung biopsies but failed to find any with these characteristic cells, although techniques of lung tissue preservation and staining may have contributed to this, and they may occasionally be seen in otherwise normal biopsies (Deutsch G, personal communication). Further case reports in term [34–36], late preterm [37,38] and preterm identical twins with twin–twin transfusion syndrome [39] followed. One case was subsequently found to have Hunter's syndrome. Interstitial glycogenosis has been identified in a patient later diagnosed with the Noonansyndrome [40]. There are no formal quantitative diagnostic criteria for the diagnosis of PIG. Glycogen is normally present in epithelial cells, including Type-II-pneumocytes, during human lung development. Mesenchymal cell glycogen may result from epithelial–mesenchymal transition [41].

Subsequent manuscripts have confirmed that PIG cells are found in multiple other conditions. Nineteen of 46 growth abnormalities in the original Deutsch classification [1] had associated partial PIG, which was much commoner than isolated PIG ($n = 6$). Further cases of this association have been described [42]. PIG has been described [43] in conjunction with abnormal alveolar development and vasculopathy, congenital heart disease, pulmonary hypertension, neuroendocrine cell excess, and congenital lymphatic and parenchymal abnormalities, including congenital thoracic malformations. In one patient with PIG cells in the setting of congenital cardiac disease [44], PIG cells had regressed on a subsequent lung biopsy. Langston et al. [3] reported that pulmonary capillaries are often reduced in number, and that patchy PIG was common in pulmonary hypoplasia (9/15 cases). Furthermore, the same abnormality was seen in 12/20 BPD patients undergoing lung biopsy. Patchy PIG was also seen in 8/16 cases with abnormalities of lung growth and alveolar acquisition, and 5/16 had pulmonary hypertension. Patchy PIG was also seen in one infant with Down syndrome and the typical alveolar growth disorder, and 3/11 biopsied for underlying cardiac disease. Overall, 33/77 patients with pulmonary growth disorders had patchy PIG, and 32 of the 55 infants younger than six months exhibited this combination. Taken together, this suggests that PIG represents a developmental disorder of fibroblast differentiation [43]. Further research has demonstrated that the cell of origin of glycogen positive cells is the pulmonary lipofibroblast [44]. In this series of five patients, four also had alveolar growth disorders, three had pulmonary hypertension and one lymphangiectasia. Three were late pre-term or early term deliveries. In a further series, in addition to cases classified as predominantly PIG, minor features of PIG were seen in three cases of congenital lobar emphysema as well as being a minor component in patients with predominant vascular disease and other interstitial pneumonias [43,45].

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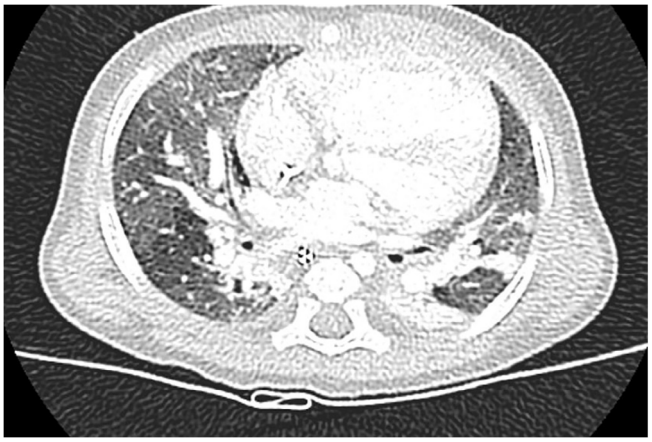

Fig. 4. HRCT appearances of pulmonary interstitial glycogenosis (PIG). There is ground glass opacification, consolidation and hyperinflated secondary lobules.

The radiographic abnormalities are nonspecific and tend to be dominated by the severity of the lung growth disorder. HRCT demonstrates variable degree of distortion of the lung architecture with linear and ground-glass opacities together with hyperinflated or hyperlucent areas (Fig. 4). This again suggests that PIG is secondary to an alveolar and vascular maturation disorder. So in summary, we believe that PIG cells are a marker of dysmaturity of the foetal mesenchyme, which may be isolated, or associated with other maturational disorders.

DYSMATURATION OF THE FOETAL PULMONARY VASCULATURE

The foetal pulmonary vascular resistance (PVR) is high, leading to physiological right to left shunting because the foetal lung has no gas-exchange function. Reflecting this, there is substantially more muscularisation of the distal pulmonary arteries and arterioles than in childhood. Furthermore, the greatly reduced numbers of alveoli in the foetal lung compared to the mature lung contributes to the elevated PVR. At birth, as the lung expands with the first breaths, PVR normally falls and there is subsequent remodelling, including regression of distal arterial tree smooth muscle, and increasing alveolar numbers. The drop in PVR is initially acutely reversible but the subsequent structural changes including thinning of the walls of the arterial tree and regression of distal smooth muscle mean that any subsequent rise in PVR due to disease is more gradual [46–49]. There are numerous causes of the acute presentation of pulmonary hypertension in the newborn period, and many recover with supportive treatment and do not enter the spectrum of chILD.

The classical primary developmental circulatory conditions characterised by dysmaturation of the foetal pulmonary vasculature are the spectrum of congenital acinar dysplasia, alveolar capillary dysplasia and the less well characterised congenital alveolar dysplasia (also sometimes called *congenital mesenchymal dysplasia*).

Congenital acinar dysplasia

Congenital acinar dysplasia is a rare, severe condition characterised by a complete lack of alveolar development [50–55]. It is seen in term or premature babies who are cyanosed at birth and survive only a few hours. It is usually associated with cardiovascular anomalies and dermal hypoplasia. The lungs are small and firm. Microscopically, bronchial-type airways that have cartilage, smooth muscle and glands are separated by abundant mesenchymal tissue. Pulmonary arteries show hypertensive changes.

Alveolar capillary dysplasia

Some cases are caused by known specific single-gene mutations [56]. The pathological features in the pulmonary circulation include scarcity of capillaries adjacent to alveolar epithelium, distended veins within the bronchovascular bundle, and medial thickening of small muscular arteries. The so-called misaligned pulmonary veins have been shown to be dilated bronchial veins by detailed morphometric reconstructions [57,58] Although these may be monogenic disorders, abnormalities are not confined to the pulmonary circulation, and immature alveolar development is an associated finding [74,75]. *STRA6* mutations and ACD were associated both with alveolar hypoplasia and pulmonary hypertension in two kindreds [59]. These conditions, which are likely part of the same spectrum [60,61], usually present with relentlessly progressive respiratory failure in term newborns and early death. Associated congenital abnormalities, including cardiac, gastrointestinal, genitourinary, limb and ocular malformations are present in 80% cases [62,63]. A baby with both a congenital pulmonary airway malformation (CPAM) and ACD has been described [64].

However, it is clear that this is a diverse spectrum of conditions. More than 10% may present late (at several months of age) [65–69]. More prolonged survival has also been described [70–73], for example with only patchy disease (which may be missed on lung biopsy [76]) despite the presence of a heterozygote *FOXF1* frame shift mutation [60]. These children have a clinical, physiological and radiographic pattern of diffuse parenchymal lung disease, suggesting that dysmaturation is not limited to the vascular tree.

An intriguing report documented an overlap syndrome in two term infants, who died 2 and 2.5 months of age [77]. Autopsy showed severe muscularisation of pre-acinar and intra-acinar pulmonary arteries and the normally non-muscularised precapillary vessels lying within the alveolar walls; there were some relatively minor intimal changes. There was some evidence of misalignment of the pulmonary veins, suggesting these two babies could have been part of the ACD spectrum. It was suggested that PVR never normalised after birth, and subsequently rose progressively.

The understanding of PHT in other early onset chILD is difficult. The potential relationships are complex; (a) PHT may be secondary to, and a direct consequence of, a reduction in the pulmonary vascular bed in growth or structure disorders; (b) PHT may be secondary to hypoxia; (c) PHT may actually be disproportionate to the changes of chILD and/or hypoxia, and be a manifestation of persistence of the foetal vasculature (generalised or patchy ACD spectrum). Finally, systemic steroid therapy, which has the beneficial effect of maturing the surfactant system, on the basis of animal data may contribute to alveolar hypoplasia and thus pulmonary hypertension [78].

Congenital alveolar (mesenchymal) dysplasia

This term has been used to describe patients where there are features of PH, lack of alveolar growth and PIG, with no predominance in any anatomic compartment. Indeed, growth abnormalities are commonly (74%) associated with histological changes of PHT [1], usually in the setting of prematurity or congenital heart disease. Histological changes of PHT were found in 74% of patients with pulmonary growth disorders outside the setting of prematurity, although the extent to which these simply related to hypoplasia of the alveolar-capillary bed is unclear. Greatly increased alveolar size and pulmonary hypertensive changes were associated with a worse prognosis.

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Table 1
Additional associations of pulmonary interstitial glycogenosis (PIG).

Gestational age	Age at presentation	Associated conditions	Outcome
Term	Birth	Severe PHT Cardiomyopathy	Died age 71 days [85]
Case 1 Term	Birth	Transposition of the great arteries	Arterial switch, discharged well on hospital day 24 [86]
Case 2 Term	37 days of age	PHT (NO treatment) Left atrial isomerism, DORV, VSD, complex abnormal venous anatomy Severe PHT	Surgical correction, discharged oxygen dependent at hospital day 39
Term	Birth	Transposition of the great arteries Severe PHT	Discharged well day 61 of life [87]
Term	One month of age	Window duct ASD Alveolar growth defect with alveolar simplification Bilateral aniridia	Well age one year [88]
38 + 4 weeks	Birth	Severe alveolar growth abnormality with alveolar simplification and enlargement	Out of oxygen and well age 18 months with residual HRCT changes [42]
34 + 5 weeks	Birth	Chylothoraces Noonan's syndrome Alveolar growth abnormality	Still oxygen dependent at one year of age [40]
38 weeks	Day 1 of life	Fetal lung interstitial tumour which contained PIG cells Normal surrounding lung	Well aged 15 years [89]

Abbreviations: ASD, atrial septal defect; DORV, double outlet right ventricle; HRCT, high resolution computed tomography; NO, nitric oxide; PHT, pulmonary hypertension; VSD, ventricular septal defect.

Aetiology of dysmaturation of the foetal pulmonary vasculature

To what extent dysmaturation of the foetal vasculature complicates other infant chILD is unclear. The case reports of PIG associated with PHT (Table 1 and above) were largely in babies with cardiac lesions known to be associated with PHT even in the absence of PIG. In a recent systematic review of PHT and chILD [79], pathophysiology could not be determined, although PHT was associated with a worse prognosis [79]. There were no systematic studies to determine the prevalence (if at all) of PHT in the alveolar growth disorders.

The classical surfactant protein gene mutations (*SpB, SpC, ABCA3*) can also be considered a manifestation of failed maturation, in this case failure to produce normal surfactant protein. These too may be associated with alveolar growth disorders [1,4] and even severe pulmonary hypertension which may have similarities to ACD [80–82]. So these are other examples of a monogenic disorder with ramifications outside a single component of the developing lung.

CONCLUSIONS

Just as elsewhere it has been argued that deconstructing the airway is a good way to approach treatment [83], here we advance the hypothesis that growth and maturational disorders should be deconstructed into dysregulated development of alveoli, airway, mesenchyme and pulmonary circulation. This is a controversial

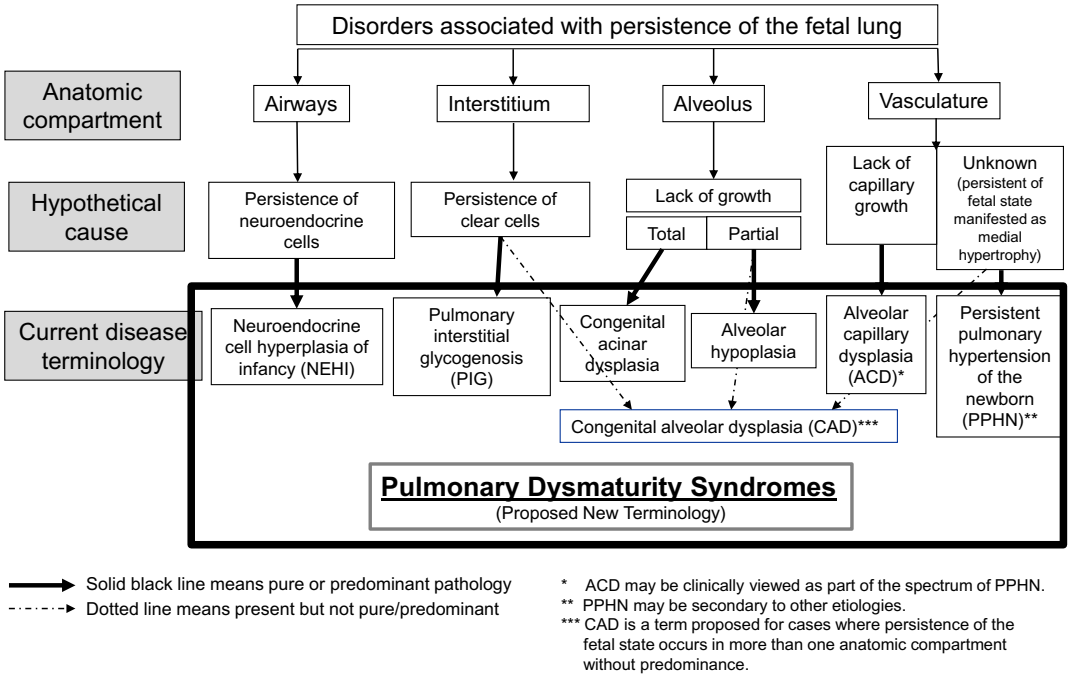

Fig. 5. Summary figure of overlapping lung dysmaturity syndromes.

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hypothesis which requires testing. Perhaps these should be called 'lung dysmaturation syndromes' if lung tissue is available, specifying which compartment(s) are affected. As with other patterns of chILD (desquamative interstitial pneumonia, and non-specific interstitial pneumonia for example), there are likely multiple different underlying genetic and environmental causes. If lung tissue is not available and the infant is running a relatively benign course with no evidence of surfactant protein or cardiovascular disorders, the term 'persistent tachypnoea of infancy' should be used [25]. We suggest that NEHI and PIG part of the 'lung dysmaturation syndromes', not discrete entities, dysmaturation of the foetal airway, and dysregulated development of the foetal mesenchyme respectively. In particular, the description of a clinical scenario or biopsy as being 'NEHI' should be the start of a diagnostic journey to determine which of many potential genes are the underlying cause. The vascular compartment remains the most difficult to classify as changes may be secondary rather than primary, and also may be minor or the dominant feature. Furthermore, pathology can be limited to the arteries with no capillaries, have a dearth or absence of capillary growth or be associated with complete absence of alveolar structures. We should quantify the extent of disease so as to identify what is prognostically important and to inform future management (Fig. 5). Finally, as in adult ILD, these diseases may be primary or secondary and in children, specific underlying gene defects should be sought. Indeed, some patterns, such as CAD, are already reported as being associated with surfactant protein disorders. In the future, progress is most likely when specific gene defects are diagnosed, and specific targeted therapies designed [84].

DIRECTIONS FOR FUTURE RESEARCH

1. Determine the spectrum of genes important in antenatal lung development, in which mutations may present as interstitial lung disease.
2. By moving from identification of histological patterns to underlying gene mutations, to move from non-specific or no therapies to specific, targeted molecular treatments for these conditions.

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