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Pulmonary interstitial glycogenosis – A systematic analysis of new cases

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ABSTRACT

Background: Pulmonary interstitial glycogenosis (PIG) is a rare paediatric interstitial lung disease of unknown cause. The diagnosis can only be made by lung biopsy. Less than 100 cases have been reported. Clinical features, treatment and outcomes have rarely been assessed systematically in decent cohorts of patients.
Methods: In this retrospective multicentre study, the clinical presentation, radiologic findings, pattern of lung biopsy, extrapulmonary comorbidities, treatment and outcome of eleven children with PIG were collected systematically.
Results: 10/11 children presented with respiratory distress immediatly after birth and 8/11 needed invasive ventilation. In 8/11 children extrapulmonary comorbidities were present, congenital heart defects being the most common. 7/11 children received systemic glucocorticoids and of these four showed a clear favorable response. During a median follow-up of 3.0 years (range 0.42–12.0) one child died, while 10 patients improved. Chest CT-scans showed ground-glass opacities (7/10), consolidations (6/10), linear opacities (5/10) and mosaic attenuation (4/10) without uniform pattern. Besides interstitial thickening related to undifferentiated glycogen positive mesenchymal cells all tissue samples showed growth abnormalities with reduced alveolarization.
Conclusions: PIG is associated with alveolar growth abnormalities and has to be considered in all newborns with unexplained respiratory distress. Apparent treatment benefit of glucocorticosteroids needs to be evaluated systematically.

1. Introduction

Children's interstitial lung diseases (chILD) cover a heterogenic group of rare paediatric disorders that mainly affect the lung parenchyma and lead to impaired alveolar gas exchange. The leading symptoms are tachypnea, hypoxemia, retractions, crackles and failure to thrive [1]. There are only limited data on the frequency of chILD; previous studies reported an incidence of 0.1–16 per 100.000 children per year and a prevalence of 1.3–3.6 per million children [2–4]. The current categorisation system of chILD lists four groups that are more prevalent among infants than in older children or adults: “Diffuse development disorders of the lungs”, “Abnormalities of alveolar growth”, “Disorders related to surfactant dysfunction “and “Conditions of undefined etiology” [3,5]. The latter comprises the diseases persistent

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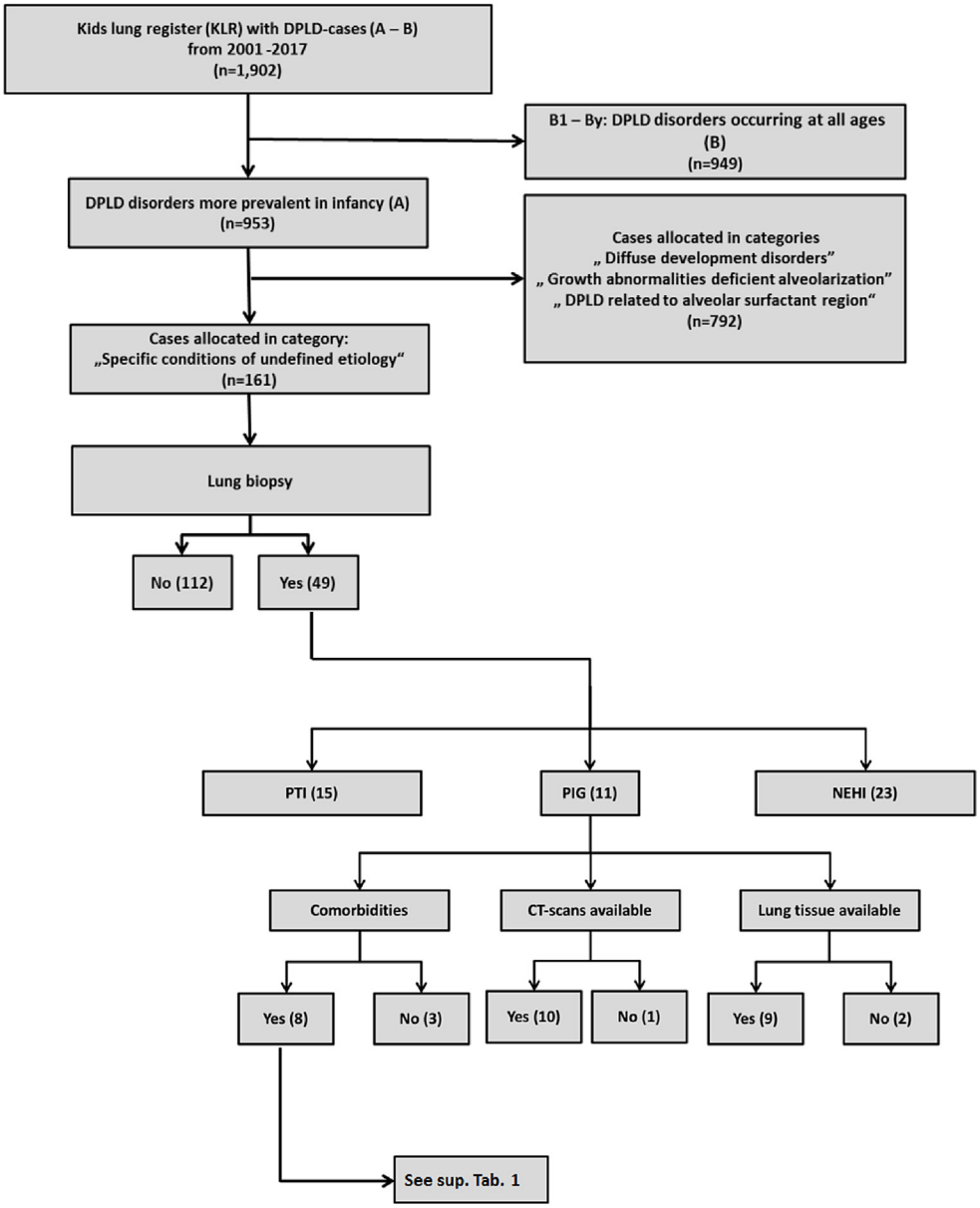

Fig. 1. Subject allocation flow. Definition of abbreviation: DPLD = diffuse interstitial lung disease, PTI = persistent tachypnoe of infancy, NEHI = Neuroendocrine cell hyperplasia of infancy, PIG = Pulmonary interstitial Glycogenosis, CT = computed tomography.

tachypnoe of infancy (PTI), neuroendocrine cell hyperplasia of infancy (NEHI) and pulmonary interstitial glycogenosis (PIG) [3,5,6].

PIG was first described 15 years ago in 7 cases with chILD [7] as the more comprehensive description of the disease "cellular interstitial pneumonitis" that was described in 1992 [8,9]. Clinically neonates and infants rapidly develop respiratory distress and hypoxemia without signs for an infection. The diagnosis can only be made by a lung biopsy showing expansion of the intersitium by spindle-shaped cells containing periodic acid-Schiff (PAS) positive diastase labile material consistent with glycogen [8]. The histopathological pattern defining PIG can exist in a patchy or diffuse distribution [7,10–12]. These characteristic phenotypes can be found in lung biopsies of patients independent of gestational ages [7,8,10,11,13–16]. Notably, histologic and ultrastructural studies of developing human lungs found no evidence of glycogen accumulation in interstitial cells at any stage of lung development [7,17]. However, cytoplasmic glycogen can be found in epithelial cells early during fetal lung development of humans and primates [7,17–19]. While underlying mechanisms resulting in the pathologic changes characteristic for PIG remain unspecified, anomalous accumulation of glycogen suggests defective maturation of mesenchymal cells [5,20] and there is an ongoing debate whether PIG reflects a non-specific reactive process secondary to different underlying diseases or is a specific developmental abnormality with aberrant differentiation [11–13].

Beside a recent large series of 28 cases focusing mainly on the histopathology, 26 cases from single case reports or collections of few cases with variable information regarding the clinical presentation, course, radiology, histopathology, and comorbidities are published.

Table 1
Clinical status and organ involvement in patients diagnosed with PIG.

Patient-ID	Sex	Gestational age	Other organ involvement	PHT	Age (yrs) and health status at last follow up
Patient A	f	term	Mucopolysaccheridosis (M. Hunter), abdomen (umbilical hernia)	yes	12, sick-better on room air, recurrent respiratory infections, reduced exercise toleance
Patient B	m	term	Mucopolysaccheridosis (M. Sanfilippo), heart (PDA)	yes	4.5, sick-better on room air, recurrent respiratory infections, reduced exercise tolerance
Patient C	m	term	Heart (VSD, PFO), brain (divided plexus)	yes	4.75, healthy
Patient D	m	term	None	yes	1.25, dead
Patent E	m	34 weeks	Brain (encephalopathy, hearing impairment), abdomen (hepatic cysts)	no	3.0, sick-better on room air, tachypnoe at rest
Patient F	f	term	None	yes	1.0, healthy
Patient G	m	30 weeks	Heart (PDA), metabolic disease (hypoglycaemia, hyperbilirubinemia)	no	3.88, sick-better on room air, recurrent respiratory infections
Patient H	f	term	None	yes	5.25, healthy
Patient I	m	term	Heart (AVSD) abdomen (inguinal hernia)	yes	1.0, healthy
Patient J	f	term	Heart (aortopulmonary fenestration, VSD, ASD hypoplastic pulmonary arterial system), kidney (megaureter on left side, renal failure)	yes	0.42, healthy
Patient K	m	term	Heterotaxy syndrome involving heart (ASD, VSD, coarctation), abdomen (intestinal malrotation, polysplenia, atypical abdominal vasculature), structural lung defect (anatomical left lung on left and right side with bronchomalacia in right main bronchus), genetically confirmed diagnosis of primary ciliary dyskinesia	yes	1.17, sick-better on room air, tachypnoe at rest

Definition of abbreviation: yrs = years, PHT = pulmonary hypertension, f = female, m = male, PDA = persistent ductus arteriosus, VSD = ventricular septal defect, ASD = atrial septal defect, AVSD = atrial-ventricular septal defect, MI = mitral valve insufficiency, “sick – better” is defined as signs any symptoms of the disease having weakened in intensity and/or number (e.g. tachypnea, but no oxygen demand”, ”sick – same” is defined as same signs and symptoms with same intensity and number.

Here we address the phenotype of PIG in a cohort of pediatric patients systematically and in depth.

2. Methods

2.1. Study cohort

The Kids Lung Register collects cases of rare paediatric lung disorders, with a focus on diffuse lung diseases (www.kids-lung-register.eu) [5]. The diagnosis of chILD is made in accordance with the American Thoracic Society [1] and European management platform [21]. Clinical information was collected retrospectively from the charts and all patients' files were updated for follow up information in 2017.

Children with histologically confirmed PIG reported to the Kids Lung Register with sufficient datasets for analysis were identified and included in this study. Demographic data, information on the clinical presentation, radiological findings, histological pictures, co-morbidities, time from symptom start to diagnosis, treatment and outcome were collected. The data on genetic diagnostics were noted.

2.2. Radiological characterization

Chest computed tomography (CT) scans were evaluated systemically by a pediatric radiologist with expertise in chest imaging especially in interstitial lung diseases. CT images were examined for the presence of parenchymal abnormalities (like mosaic attenuation, ground glass opacity, consolidation, linear opacity, septal thickening, reticular opacity, crazy paving, nodular opacity, honeycombing, emphysema, cysts, bleb or bulla) and airway abnormalities (tree-in-bud, bronchiectasis, bronchial wall thickening) [22] on a lobar basis (counting lingula as the separate lobe) as well as for the presence of pleural and mediastinal abnormalities (pleural effusion, pleural thickening, enlarged heart, enlarged mediastinal or hilar lymph nodes).

2.3. Lung biopsy

The diagnosis of PIG was made if interstitial thickening was present due to accumulation of immature interstitial cells containing abundant cytoplasmic glycogen defined by a periodic acid-Schiff (PAS) positive diastase. If more than half of the interstitial tissue was thickened, the pattern was defined as diffuse, if less it was defined as patchy. The presence of neuroendocrine cells was determined by immunohistochemistry using bombesin staining. The width of the alveolar septa was measured for each tissue in several different locations at least 3 times. The aberration from the normal histopathological pattern and reduced alveolarization were scaled (1) mild, if the histological aberration was seen in < 10% of the lung tissue, (2) moderate, if the histological aberration affected 10–50% of the lung tissue and (3) severe, if architectural distortion was seen in > 50% of the lung tissue. Signs for pulmonary arterial hypertension were scaled according to arterial wall thickness.

2.4. Statistics

All data were analyzed retrospectively. As to the rather small number of included patients, for reliable results only descriptive statistics were performed. Values are indicated as median and ranges.

2.5. Ethics statement

All participants, their parents or caregiver provided written consent to participate in the Kids Lung Register, anonymized analysis and publication of all obtained data. The study was approved by the Ethics Commission at the Ludwig Maximilans University of Munich (EK 026–06, 257–10, 111–13).

Table 2
Clinical characterization and outcomes (n = 11).

Characteristics	
male	7
preterm birth[a]	2
Clinical findings after birth	
Onset of symptoms within the first day of life	10[b]
Onset of symptoms with Tachypnoe	11
Retractions	9
Crackles on auscultation	2
Ventilatory support	
Oxygen supplementation need at any time	11
Non-invasive ventilation need at any time	9
Invasive ventilation need at any time	8
Other organ involvement	10
Structural heart disease	6
VSD	1
PDA	2
AVSD, ASD	1
ASD, VSD, atypical lung venous return	1
Aortopulmonary fenestration, VSD, ASD, hypoplastic pulmonary arterial system	1
Pulmonary arterial hypertension (echocardiography)	9
Clinical findings at last follow up	
Age, yrs	3.5 (0.42–12.0)
Health status[c]	
healthy	5
sick – better[d]	5
sick – same	0
dead	1
Age since when the health status exists (yrs)	1.5 (0.08–3.88)
Age of last follow up (yrs)	3.0 (0.42–12.0)
Medication	
Steroids (systemic)	7
Therapy helped	4

Data are presented as number of cases or median (range).
Definition of abbreviation: PDA = persistent ductus arteriosus, ASD = atrium septum defect, VSD = ventricular septum defect, AVSD = atrio-ventricular defect, yrs = years.
For the detailed clinical characteristics of all patients see supplementary file (Table 1 supp. clinical status and organ involvement).

[a] Two patients born after 30 and 34 weeks of pregnancy (Patient G and Patient E).

[b] One patient showed the first symptoms with 7 weeks (Patient I).

[c] "Sick – better" is defined as signs any symptoms of the disease having weakened in intensity and/or number (e.g. tachypnea, but no oxygen demand), "sick – same" is defined as same signs and symptoms with same intensity and number.

[d] All patients characterized as "sick – better" show stable oxygen-saturations on room at rest, but have tachypnoic phases and a reduced exercise tolerance.

3. Results

3.1. Study population

Between 2001 and 2017, a total of 1902 children with chILD were included in the Kids Lung Register. Of those, 116 children were categorized to the group "Specific conditions of undefined etiology". Among them 11 patients with histological proven "Pulmonary interstitial glycogenosis" were identified (Fig. 1). Parts of the clinical data from one patient (Patient A) have been published as case reports [23,24]. Surfactant dysfunction syndromes were ruled out by genetic tests in six patients (mutations in genes coding for ABCA3 in five, SFTPC in six and SFTPB in three children).

3.2. Clinical characteristics on presentation

Detailed information on demographic data and clinical symptoms of the patients are listed in Table 1 and Table 2. Except for two preterm infants (34 and 30 weeks of gestational age) all patients were term neonates, seven were male. Ten children were symptomatic directly after birth and one developed symptoms at the age of seven weeks. At first presentation tachypnea and hypoxemia was present in all children, retractions in nine and inspiratory crackles on auscultation in two. Eight children needed invasive and one non-invasive ventilation due to respiratory failure. Relevant extrapulmonary comorbidities were reported in eight patients (Table 1). Six patients were diagnosed with congenital heart defect: Persistent ductus arteriosus (Patient B and Patient G), ventricular-septal defect (Patent C), atrial-ventricular septal defect in combination with atrial septal defect (Patient I), aorto-pulmonary fenestration, ventricular-septal defect, atrial septal defect and hypoplastic pulmonary arterial system (Patient J) and ventricular-septal defect, atrial septal defect and coarctation (Patient K). In nine patients pulmonary arterial hypertension was diagnosed by echocardiography. Two patients (Patient A and B) were diagnosed with metabolic diseases (Morbus Hunter, Morbus Sanfilippo) and one with heterotaxy-syndrome due to genetically confirmed primary ciliary dyskinesia (Patient K).

3.3. Clinical presentation at follow up

The median follow up was time 3.0 years (range 5 months–12 years). After a median time of 1.25 years (range 29 days to 3.88 years) the respiratory condition of ten children significantly improved compared to baseline. One child died at the age of 1 year and 3 months. It was the only child whose respiratory situation did not improve. He was discharged from the hospital with a tracheal cannula and needed mechanical ventilation. He died after a respiratory infection with a Rhinovirus. At last follow up five children were asymptomatic while the other five patients still had some respiratory symptoms (tachypnoea and a reduced exercise tolerance). None required supplemental oxygen at rest (see supp. Table 1).

3.4. Medication

Seven children received systemic corticosteroids (see supl. Table 1). Five children received pulse therapy (Methylprednisolon 10 mg/kg/d on three days or Predniolone 50 mg/kg on 4 days), the other two continuous treatment (Predniolone 2 mg/kg/d). The start of the treatment differed broadly (range 2–74 days after start of the first respiratory symptoms). For four patients an improvement of the respiratory situation after therapy was documented (3x pulse, 1x continuous therapy). Two patients (Patient H and Patient J) were successfully extubated, one (Patient C) weaned of the non-invasive ventilation and one patient (Patient I) showed reduced oxygen demand on oxygen template.

Four patients received hydroxychloroquine (Patient D, E, G and J). For none of them a positive response is documented.

3.5. Radiological characteristics

CT scans were done from ten patients (Fig. 2, supl. Table 2) and performed at median age of 39 days (range 7–164) (Table 3), all but one (Patient I) after start of treatment with glucocorticosteroids. All CT-scans showed signs for an interstitial lung disease. Ground-glass opacities (n = 7), consolidations (n = 6), linear opacities (n = 5) and mosaic attenuation (n = 4) were the most common findings, although no uniform pattern could be found. Septal thickening was seen in four patients and was exclusively present in the upper lobes. Less common

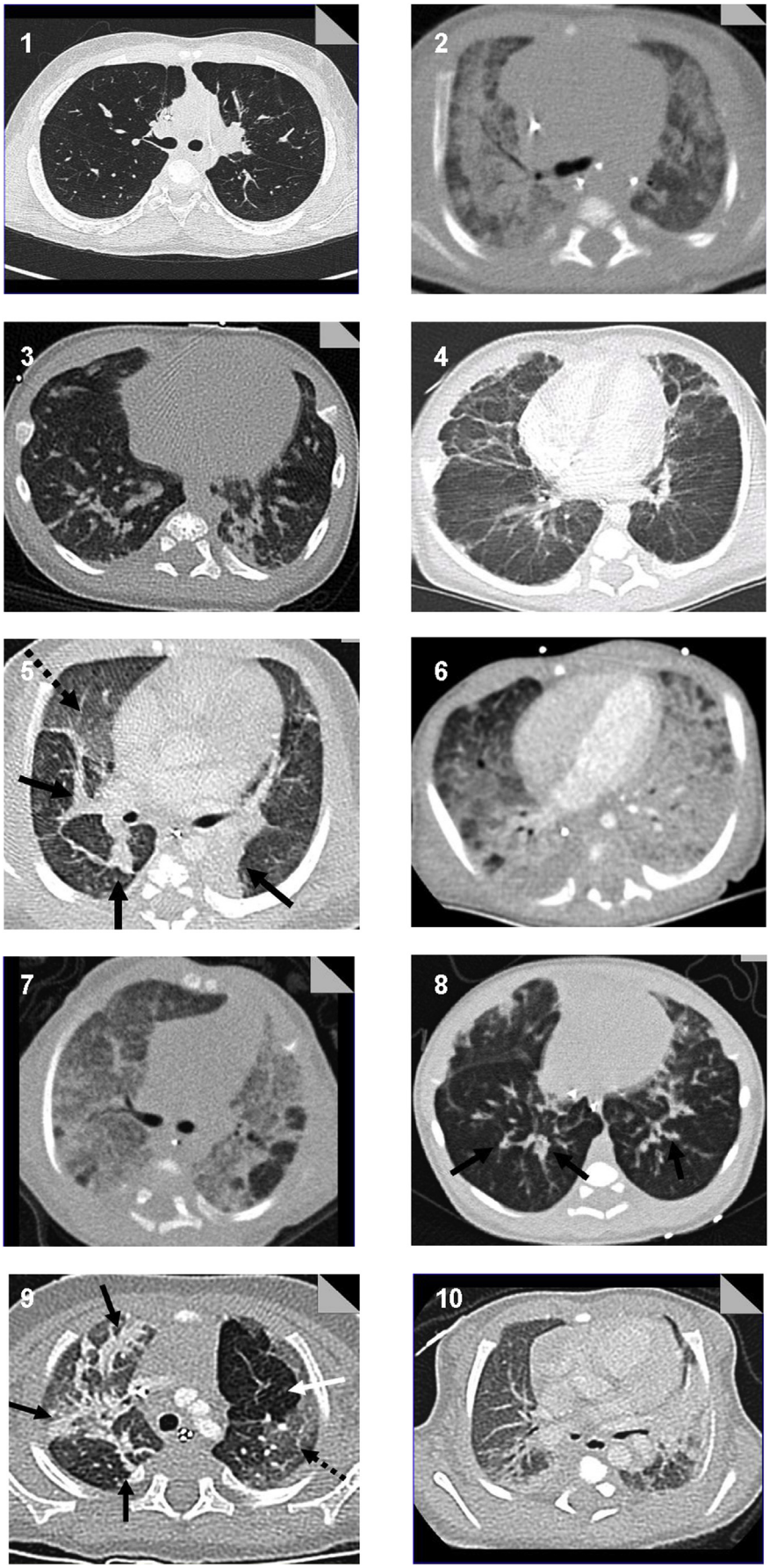

Fig. 2. (1) Patient A: Mild mosaic attenuation in both lungs and mild bronchial dilatation in the lingula; (2) Patient B: Diffuse bilateral ground glas opacity and patchy consolidations; (3) Patient C: Linear densities and focal consolidations in both lower lobes; (4) Patient D: Linear opacities/scaring in both lungs, predominantely in the middle lobe; (5) Patient E: Ground glass opacity of the middle lobe (dashed arrow), areas of consolidation in both lower lobes (arrows); (6) Patient F: Ground glass opacities and consolidations in boths lungs; (7) Patient G: Both lungs presented with crazy paving with some peripheral areas beeing preserved; (8) Patient H: Bronchial wall thickening in the lower lobes (arrows) and areas of ground glas opacities in the middle lobe and lingula; (9) Patient I: Irregular consolidations (black arrows) with ground glas opacity in the right upper lobe, ground glas opacity (dashed arrow) and hyperinflation (white arrow) in the left upper lobe; (10) Patient K: Consolidation in the left upper lobe and dorsal atelactasis

Table 3
Chest CT Findings (median age at scan 30 days (range 7–164), n = 10).

	UL	ML or L	LL
	right/left	right/left	right/left
Findings			
GGO	7/7	6/6	6/6
Consolidation	5/6	4/3	5/5
Mosaic attenuation	4/3	2/2	4/4
Linear opacity	3/4	3/3	5/5
Septal thickening	4/2	−/−	−/−
Hyperinflated secondary lobule	−/−	2/-	1/1
Emphysema	-/1	−/−	-/1
Crazy paving	1/1	−/−	−/−
Reticular or nodular opacity, honey combing, cysts	−/−	−/−	−/−
Airways			
Bronchiectasis	-/1	1/-	−/−
Architectural distortion	1/1	1/1	1/1
Bronchial wall thickening	1/1	1/1	1/1
Tree in bud	−/−	−/−	−/−
Pleura			
Pleural effusion	1/1		
Pleural thickening	−/−		
Mediastinum			
Heart enlarged	2		
Enlarged med. lymph nodes	–		
Enlarged hilar lymph nodes	1		

Data are presented as number of cases.
Definition of abbreviation: GGO = Ground Glass Opacities, UL = upper lobe, ML = middle lobe, L = lingula, LL = lower lobe, med. = mediastinal

Table 4
Histopathology (median age at biopsy 53 days (range 7–176), n = 9)[a].

Width of alveolar septa (mm)	0.03 ± 0.01 (0.01–0.05)
Aberration from normal histological pattern	
mild	1
moderate	8
severe	–
PIG pattern	
diffuse	8
patchy	1
Reduced alveolarization	
mild	4
moderate	1
severe	4
NEH (> 10% NEC)*	4
Suspected pulmonary arterial hypertension (due to thickened arterial wall)	
mild	5
moderate	2
severe	2

Data are presented as number of cases,
Definition of abbreviations: NEH = Neuroendocrine cell hyperplasia, NEC = neuroendocrine cells.
*Bombesin stain only made in 5 patients.
[a] Lung tissue for reference pathology was available only form 9 patients.

were a hyperinflated secondary lobe (n = 2), emphysema (n = 1) and crazy paving pattern (n = 1). Absent in all patients were reticular or nodular opacities, honey-combing and cysts.

In two cases both with diagnosed heart disease (Patient I and K) the heart was enlarged. One patient had a pleural effusion (Patent E). Pleural thickening was observed in none of the cases.

3.6. Histopathology

Of the eleven included patient nine biopsies were available for a histological review by a pathologist specialised in interstitial lung diseases (Table 4, Fig 3, sup. Table 2). The tissue of the other two biopsies was not available for re-evaluation. All analysed samples showed expansion of the interstitium by spindle-shaped cells containing periodic acid–Schiff positive, diastase labile material consistent with glycogen. In two cases the deviation from a normal histological pattern was rated as mild and in seven cases as moderate, never as severe or normal. The expanded interstitium had a width of 30 µm (range 10–50). In eight cases the PIG-pattern was described as diffuse, only in one as patchy. To identify growth abnormalities, reduced alveolarization, pulmonary artery hypertrophy, numbers of neuroendocrine cells (NEC) were investigated. In five samples Bombesin staining was possible and performed. As described in Rauch et al. [6] NECs were evaluated as increased, if over 10% of total bronchiolar cells were NECs. Four samples fulfilled this criterion (range 11%–17%), the other had a value just below the cut off (9%). All tissue samples had signs of reduced alveolarization and a hypertrophy of the lung vessels as a sign for arterial hypertension. Reduced alveolarization was rated as mild in 4, as moderate in 1 and as severe in 4 samples. The hypertrophy of the lung vessels were rated as mild in 5, as moderate in 2 and as severe in 2 samples.

3.7. Correlation

In this cohort, we did not find a correlation between the severity of clinical presentation and outcome, radiological changes or histopathologic characteristics (see Suppl. Table 2). Of interest, only one patient (Patent D) died. He had no other organ-involvements, a patchy distribution of PIG in the biopsy, and needed mechanical ventilation until he died from a respiratory infection. Two other patients had no other organ involvement, both needed invasive ventilation and are asymptomatic at follow up.

For the treatment with systemic glucocorticosteroids very different protocols were used. In four children the respiratory situation improved, in three not. Three were effectively treated with pulsed corticosteroids and one with continuous glucocorticosteroids, whereas in two patients the pulsed and in one patient the continuous treatment was ineffective. Three children with congenital heart disease (Patient E, Patient H and Patient J) were successfully treated, one patient with congenital heart disease (Patient G) not (sup. Table 2).

One preterm born child (Patient G) and one with diagnosed Mucopolysaccharidosis (Patient A) did not improve after treatment with glucocorticosteroids. The other preterm patient (Patient E) and child with diagnosed Mucopolysaccharidosis (Patient B) did not receive a treatment with systemic corticosteroids.

4. Discussion

In this study we have systematically analysed a cohort of children diagnosed with PIG by a multidisciplinary team [21]. Key findings were that (1) almost all patients improved over time, (2) mostly accelerated if glucocorticosteroids treatment given, but independent of their initial presentation, CT findings or histopathological features, (3) over half of the patients were diagnosed with additional extrapulmonary abnormalities, mostly congenital heart defects and (4) all analysed lung tissues had clear signs of reduced alveolar growth.

Since the defining description by Canakis in 2002 fifty-four cases with PIG have been published [7]. Here we have reviewed and compiled all cases reported in the literature up to now (Table 5) and compare those data to the systematic findings of the present report.

Overall there was good agreement of our findings with the published data; however there were several areas of interest and novelty which we highlight below. In agreement with the published data we found an association between PIG and extra-pulmonary comorbidities or systemic diseases in more than half of the patients. Although a coincidental associations of different conditions cannot be excluded this

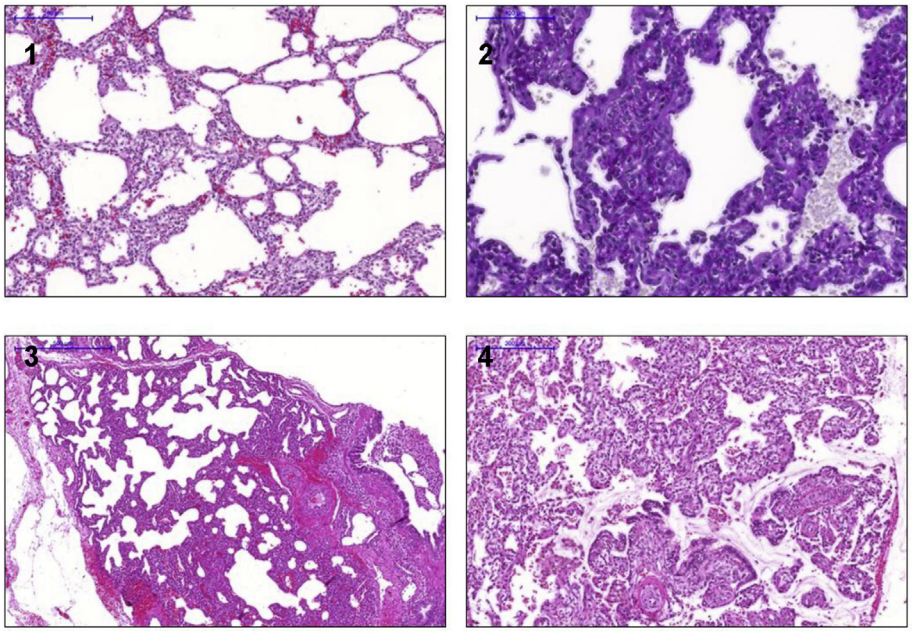

Fig. 3. (1) Wedge biopsy of Patient D showing patchy PIG with small area of normal alveolar septa in right upper corner (HE, x100); (2) Wedge biopsy of Patient D showing patchy PIG interstitial accumulation of PAS-positive glycogen containing mesenchymal cells (PAS x200), (3) Wedge biopsy of Patient H showing diffuse PIG and alveolar growth abnormality with enlarged and simplified airspaces (HE x50); (4) Wedge biopsy of Patient F showing diffuse PIG and severly thickened walls of small arteries consistent with pulmonary hypertension (HE x50).

seems unlikely due to the rarity of the single diseases. As has previously already been expressed, PIG might indicate impaired differentiation and maturation of the lungs due to different causes (publication in preparation). Thus the demonstration of PIG on histology may be a general marker of developmental dysmaturity of the pulmonary interstitial compartment and not an entity in itself.

Among the associated conditions, congenital heart defects and pulmonary hypertension were most common [11,13,16,25–29]. More importantly from a clinical point of view, mucopolysaccharidoses (MPS) were overrepresented in our cohort with two out of eleven children. A third child with PIG and MPS has recently been described in the literature [30]. In our cohort of infants with unexplained tachypnoe and suspected PIG, but without biopsy, we identified MPS type IIIB by whole exome sequencing as the underlying genetic cause (homozygote chr17:40695044_A/G). This child was subsequently weaned off oxygen and had no pulmonary complaints at 3 months when she was discharged from hospital. These data are in agreement with results from a large cohort of neonates with confirmed MPS type I. In this group of 55 patients a relevant proportion (59%) suffered from respiratory symptoms of unknown cause during the first month of life: 26% required respiratory support during the neonatal period, an additional 33% developed other respiratory symptoms (including signs of upper airway obstruction and respiratory infections) during the first month of life [31]. As a lung biopsy and histological examination of the tissue is required to establish this diagnosis, PIG may be under-recognized in patients with MPS, especially as a relevant proportion of children suffering from PIG improve over time. Therefore, an increased awareness of PIG especially in children with MPS and relevant respiratory complaints after birth could lead to an early diagnosis of mucopolysaccharidoses.

In our cohort one child (Patient K) presented with heterotaxy syndrome which was later confirmed to be related to primary ciliary dyskinesia (PCD) by genetic testing. 75–85% of all PCD patients suffer from RDS after birth and the exact causes are not yet identified [32–35]. We speculate that this could be related to the presence of PIG as it is known that respiratory cilia play a relevant role in organ development and maturation [36] and PIG may be related to lung dys-maturity, as indicated above.

Cutz et al. [11] published a systematic review of pathological findings stressing the association of PIG with a spectrum of pulmonary and cardiovascular disorders and supporting the theory of a development abnormality. In accordance, in our cohort all biopsies showed reduced alveolarization and 4 of 5 tissue samples increased NEC, the latter being also a sign of immaturity [6,11].

The CT-scans were suggestive for interstitial lung disease showing ground-glass opacities, consolidations and septal thickening, but no uniform pattern was identified. Prognosis seemed favourable as almost half of the patients were reported as healthy and in additional 21% respiratory condition was improved. Nevertheless, there was a fatal outcome in almost one third of the patients.

For the good response to systemic glucocorticosteroids we have no explanation. Lung maturation may be accelerated after glucocorticosteroids were given [37–40]. As we do not know any long-term consequences and the best treatment modalities, the benefit of systemic glucocorticoisteroids needs to be analysed in prospective controlled trials.

Limitation of this study is the retrospective nature of initial accumulation of information. Most of the subjects are now included in the Kids Lung Register and can be prospectively observed over extended time periods. Nevertheless, to enlighten the patho-mechanisms and treatment options more basic research and prospective studies are needed.

To our knowledge this is the first study to describe a detailed follow up, treatment with glucocorticosteroids and systematic evaluation of pathological and radiological changes of patients diagnosed with PIG. Our findings were put into the perspective of a review over all published cases. PIG should be included into the differential diagnosis of neonates and infants with unexplained respiratory distress, considering in particular mucopolysaccharidoses. In the presence of congenital heart defects or heterotaxia syndromes unexplained respiratory disease might be due to coexistent PIG.

Table 5
Studies on PIG cases in the literature until 2017.

Paper	Gestational age (weeks)	Gender	Age at onset of symptoms	Mechanical ventilation	Congenital heart disease (CHD)	pPHN*	Histological PIG pattern	HRCT	Treatment with Glucocortico-steriods	Outcome
Canakis et al., 2002 [7]	33	male	5 d	yes	no	ng	diffuse	normal[a]	yes	healthy
	term	male	since birth	yes	no	ng	diffuse	GGO, coarse linear bands of opacities	yes	healthy
	term	male	28 d	no	no	no	diffuse	GGO	yes	healthy
	33	male	since birth	yes	no	ng	diffuse	ng	no	sick-better
	29	female	since birth	yes	no	ng	diffuse	ng	yes	healthy
	term	male	since birth	no	no	ng	diffuse	ng	no	healthy
	25	male	since birth	yes	no	ng	diffuse	ng	yes	dead
Onland et al., 2005[14] [b]	32	male	since birth	yes	no	no	diffuse	GGO, thickened interstitial septae	yes	healthy
	32	male	since birth	yes	no	no	diffuse	GGO, thickened interstitial septae	yes	healthy
Lanfranchi et al., 2010 [20]	31	male	since birth	yes	no	ng	ng	coarse reticular opacities surrounding aerated or hypererated lungs	yes	healthy
Castillo et al., 2010 [41]	term	male	since birth	yes	no	ng	patchy	GGO, reticular opacities, interlobular septal thickening, cysts	ng	healthy
Smets et al. 2011[c] [23,24]	term	female	since birth	ng	no	yes	diffuse	GGO, architectural distortion linear opacities, overinflation, emphysema	yes	sick-better
King et al., 2011 [13]	term	male	since birth	yes	PDA, PFO	yes	ng	not done	no	dead
Radman et al., 2012 [16]	term	female	since birth	yes	transposition of great arteries	yes	patchy	not done	yes	healthy
	term	male	since birth	yes	Complex[e]	yes	diffuse	not done	no	sick-better
Alkhorayyef et al., 2013 [25]	term	male	since birth	yes	severe hypertrophic cardiomyopathy	yes	diffuse	not done	no	dead
Ross et al. 2014[d] [27]	34 + 5	male	since birth	yes	pulmonary valve abnormalities	no	ng	septal thickening, extensive dependent airspace opacities, pleural effusions	yes	sick-better
Ehsan et al., 2014 [42]	term	male	since birth	yes	no	ng	diffuse	GGO	yes	healthy
Siomos et al., 2015 [28]	ng	femal	one months	no	ASD, Widow duct at the pericardial reflection on the pulmonary artery	ng	ng	no specific features	no	healthy
Jiskoot-Ermers et al., 2015 [26]	term	male	since birth	yes	PDA	yes	ng	not done	yes	dead
Deutsch et al., 2016 [43]	term	male	since birth	yes	no	ng	ng	ng	ng	sick-better
	term	male	since birth	yes	no	ng	ng	ng	ng	healthy
	term	female	since birth	yes	total anomalous pulmonary venous return/vein stenosis	yes	ng	ng	ng	dead
	35	female	since birth	yes	DORV	yes	ng	ng	ng	sick-better
	36	male	since birth	yes	no	yes	ng	ng	ng	healthy
Still et al., 2017 [29]	term	ng	ng	ng	no	yes	ng	no specific features	ng	sick-same

(*continued on next page*)

Table 5 (*continued*)

Paper	Gestational age (weeks)	Gender	Age at onset of symptoms	Mechanical ventilation	Congenital heart disease (CHD)	pPHN*	Histological PIG pattern	HRCT	Treatment with Glucocortico-steriods	Outcome
Cutz et al., 2017 [11]	term	male	since birth	no	no	ng	diffuse	not done	no	dead
	term	male	since birth	ng	PDA	ng	patchy	GGO	ng	dead
	term	female	since birth	ng	no	ng	patchy	ng	ng	ng
	32	male	since birth	ng	no	ng	diffuse	interlobular thickening	ng	ng
	term	male	since birth	ng	no	ng	diffuse	GGO	ng	dead
	term	male	ng	ng	no	ng	patchy	ng	yes	dead
	33	female	since births	ng	no	ng	diffuse	non specific features	ng	ng
	term	male	ng	ng	no	ng	patchy	ng	ng	dead
	term	female	ng	ng	no	ng	patchy	ng	ng	dead
	term	female	ng	ng	complex (right atrial isomerism, dextrocardia, AVSD,DORV, hypoplastic RPA	ng	focal	ng	ng	dead
	term	male	since birth	ng	hypoplastic left heart syndrome	yes	focal	GGO	ng	dead
	36[f]	female	ng	ng	hypertrophic cardiomyopathy	yes	ng	septal thickening, bilateral pleural effusion	ng	dead
	term	female	since birth	ng	ASD, VSD	yes	ng	siffuse interstitial lung disease	yes	dead
	term	male	ng	ng	TAPVD	yes	diffuse	GGO, septal thickening	ng	ng
	term	male	since birth	ng	no	ng	diffuse	crazy paving	ng	sick-better
	term	male	ng	ng	no	ng	ng	GGO, septal thickening	ng	sick-better
	30	male	since birth	yes	ASD, VSD	ng	ng	GGO, basal hyperinflation	ng	sick-better
	36	female	ng	yes	ng	yes	patchy	ng	ng	ng
	term	female	since birth	ng	ng	yes	focal	ng	ng	ng
	term[f]	female	ng	ng	ng	ng	ng	cysts	ng	healthy
	term[f]	female	ng	ng	ng	ng	diffuse	cysts	ng	healthy
	term[f]	female	since birth	ng	PA stenosis	ng	focal	cysts	ng	healthy
	31[f]	male	since birth	ng	ng	ng	focal	cysts	ng	healthy
	term[f]	male	since birth	ng	ng	ng	focal	cysts	ng	healthy
	term	male	ng	ng	ng	ng	focal	right middle lobe overinflation	ng	sick-worse
	term	male	2 months	no	ng	ng	focal	right middle lobe overinflation	ng	healthy
	term	male	1 months	no	ng	ng	focal	right upper lobe overinflation	ng	healthy
	term	male	1 months	no	ng	ng	diffuse	left upper lobe hyperinflation	ng	healthy
Frequencies or median	62% term	68% male	Since birth	77% mechanical ventilation	38% CHD	70% pPHN	55% diffuse 21% patchy 24% focal	32% GGO, 24% septal thickening	68% treated with glucocorticosteriods	46% healthy 21% sick-better 2% sick-same 2% sick-worse 29% dead

Definition of abbreviations: ng = information not given, GGO = ground-glass opacities, CHD = congenital heart disease, PDA = persistent ductus arteriosus, pPHN = persistent pulmonary hypertension of the newborn, PFO = persistent foramen ovale, ASD = atrium septum defect, VSD = ventricular septum defect, AVSD = artio-ventricular septum defect, DORV = double outlet right ventricle, RPA = right pulmonary artery, TAPVD = anomalous pulmonary vein connection, PA = pulmonary artery valve.

[a] Performed at the age of 5 years,

[b] both reported patients are identical twins.

[c] Later diagnosed with Hunter Syndrome (Patient A in our cohort).

[d] Later diagnosed with Noonan Syndrome,

[e] Heterotaxy syndrome (left atrial isomerism), double-outlet right ventricle, ventricular septal defect (VSD) with pulmonary stenosis with anomalous drainage of the right pulmonary veins to the right atrium, interrupted infrahepatic inferior vena cava with azygous continuation to the right superior vena cava, left superior vena cava that drained to the coronary sinus, and right sided aortic arch with an aberrant left subclavian artery.

[f] Additionally diagnosed with Congenital Pulmonary Adenomatoid Malformation.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2018.05.009.

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