CLINICAL CASE DISCUSSION ON NEONATAL INTERSTITIAL LUNG DISEASE AND INTERSTITIAL LUNG DISEASE BEFORE 2 YEARS

ERS and ESPR Joint Webinar
20 June, 2023

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Speakers: Dr Chiara Sileo, Prof. Nadia Nathan

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Paris, France

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☒ We have no real or perceived conflicts of interest that relate to this presentation.

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ERS EUROPEAN RESPIRATORY SOCIETY

NEONATAL RESPIRATORY DISTRESS

3 - 4% of newborns

Frequent causes

- Transient respiratory distress
- Maternofetal infection
- Meconium aspiration
- Effusion (pneumothorax, pneumomediastinum, chylothorax)

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Rare causes

- Cardiovascular disorders
  - Congenital heart malformation
  - Delayed decrease of pulmonary pressions
- Lung disorders
  - Malformations
    - Congenital diaphragmatic hernia
    - Esophageal atresia
    - Congenital pulmonary airway malformation
    - Others
  - Interstitial lung diseases (ILD)
  - Primitive ciliary dyskinesia / Cystic fibrosis
  - Diffuse developmental disorders of the lung
- ENR: choanal atresia, other malformations
- Neuromuscular disorders

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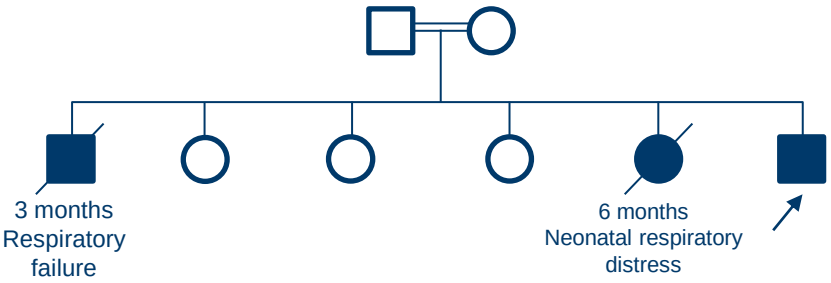
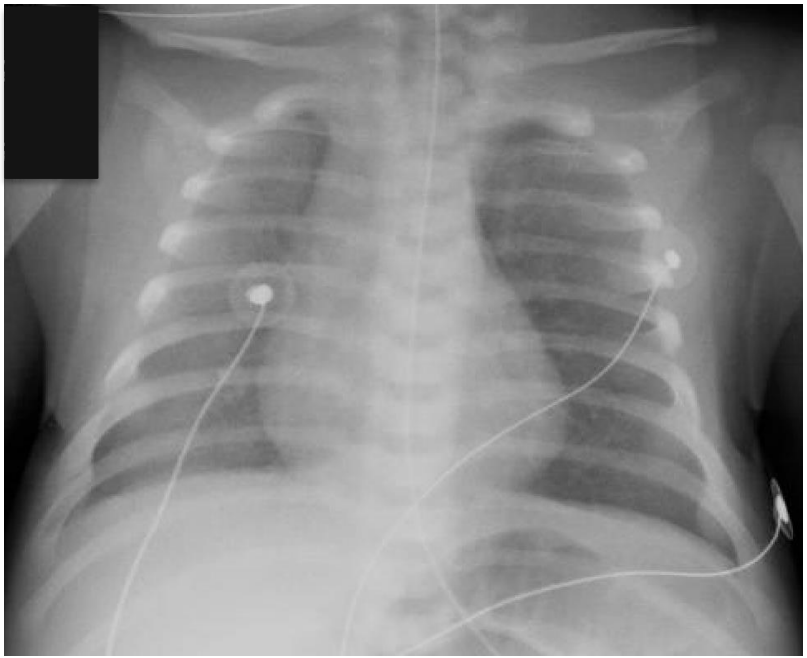
CASE 1 (M.)

- Consanguineous parents from Afghanistan
- Normal pregnancy
- Full-term neonate - 39 WG
- Normal birth weight

- Neonatal respiratory distress (H8)
- Signs of respiratory distress
- Hypoxaemia requiring oxygen support and NIV
- Pulmonary hypertension (PHT)
- Transfer to the intensive care unit

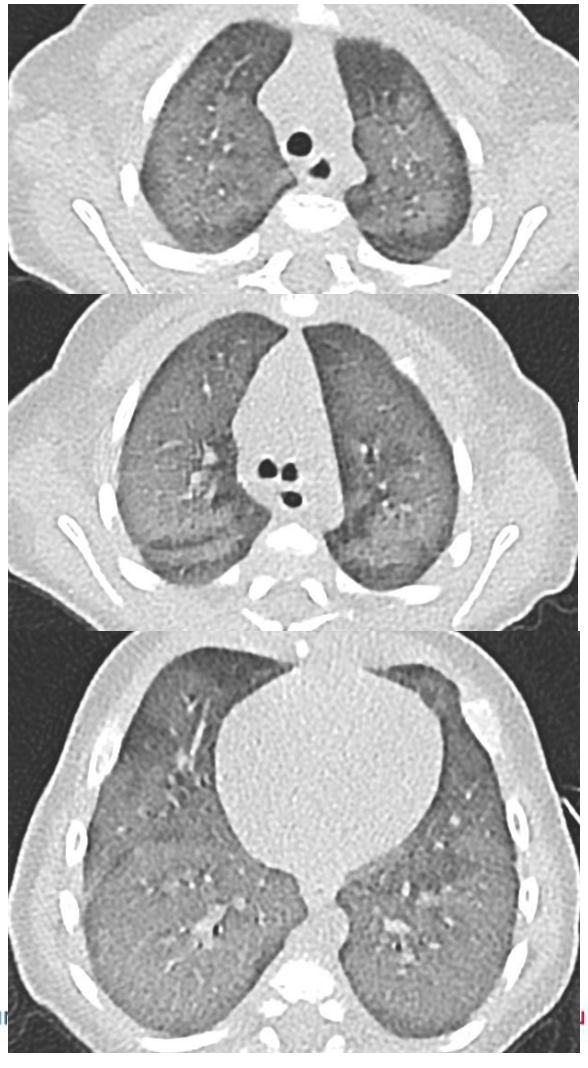




CASE 1 (M.)

- No infection
- No malformation
- No extra-respiratory disorder

- High Resolution Computed Tomography (HRCT) at 25 days



Neonatal interstitial lung disease: which one? (MCQ)

A. Chlamydia trachomatis infection
B. Surfactant protein B deficiency
C. Alveolar haemorrage
D. Alveolar capillary dysplasia
E. ABCA3 deficiency

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2010 & 2018 childhood ILD (chILD) classification

ILD related to exposure/environment insults	ILD related to systemic diseases processes	ILD related to lung primary parenchyma dysfunctions	ILD specific to infancy
Hypersensitivity pneumonitis	Connective tissue diseases	Surfactant disorders	Neuroendocrine cell hyperplasia of infancy
Medication, Drugs Radiation exposure	Vasculitis	Diffuse alveolar hemorrhages	Pulmonary interstitial glycogenosis
	Granulomatous disorders	Eosinophilic lung diseases	Diffuse developmental disorders
	Metabolic disorders	Lymphatic disorders	
		Viral infections	

Nathan et al. Expert Rev Respir Med 2018
Chronic interstitial lung diseases in children: diagnosis approaches

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Pros : Consanguinity
Cons : Neonatal onset
No hepatomegaly
No splenomegaly
No hypotonia

Nathan et al. Expert Rev Respir Med 2018
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Neonatal onset
No extra-respiratory disorder
CT pattern
PHT
Cons:

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Pros: Neonatal onset
Cons: No congenital heart disease

Pros: Neonatal onset
PHT
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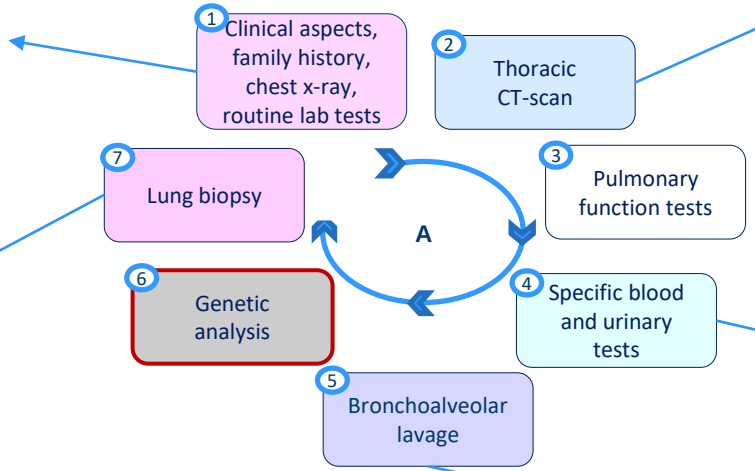
CT pattern

Diagnostic workup in chILD

Consanguinity
Neonatal onset
No extra-respiratory disease

Diffuse dense GGO
Moderate signs of PHT
No crazy paving



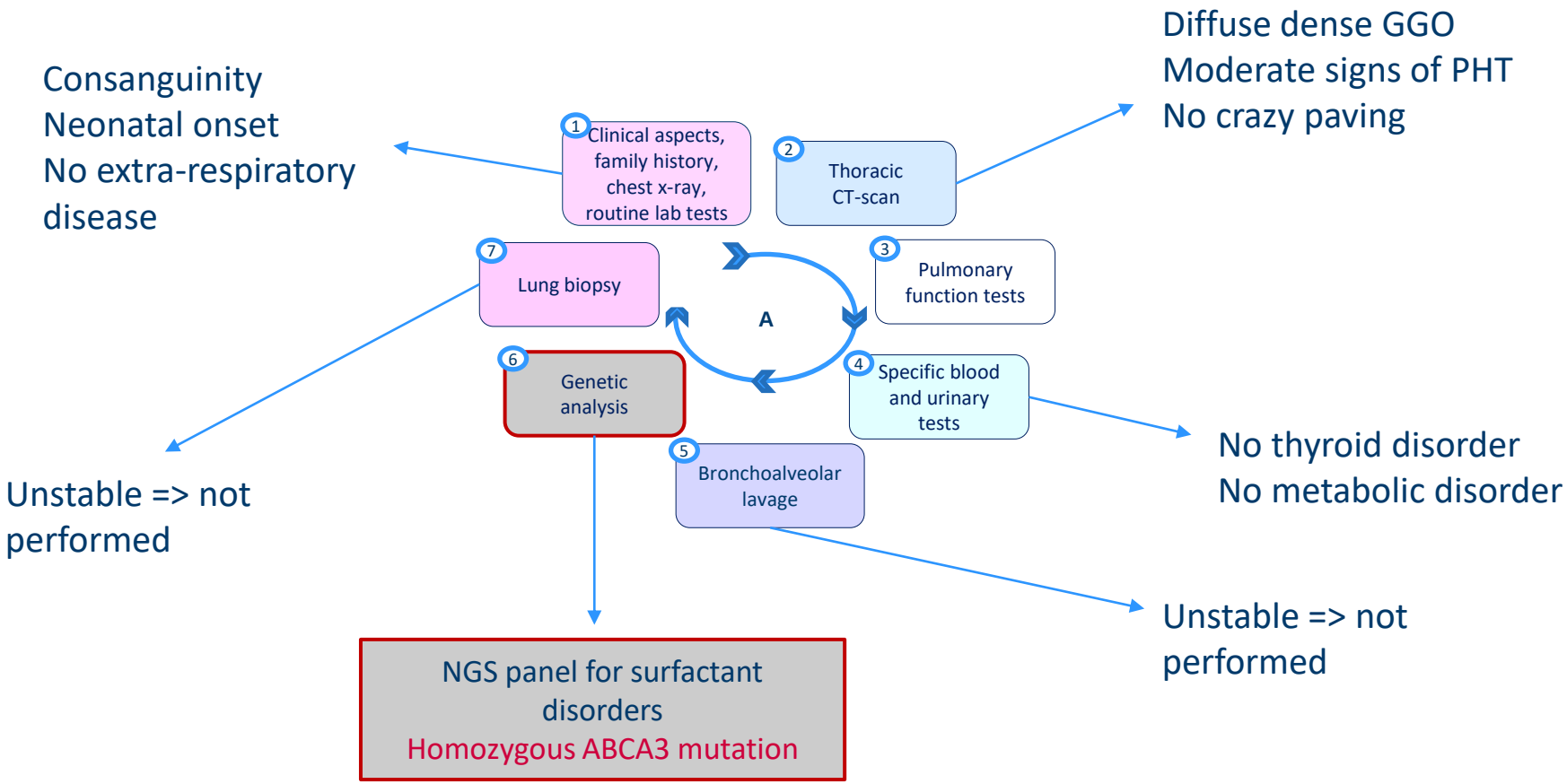
Unstable => not performed

No thyroid disorder
No metabolic disorder

Unstable => not performed

Nathan et al. Eur Respir Rev 2023

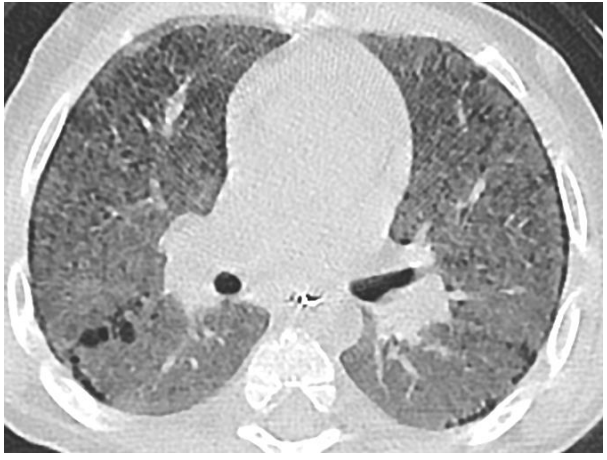
Diagnostic workup in chILD



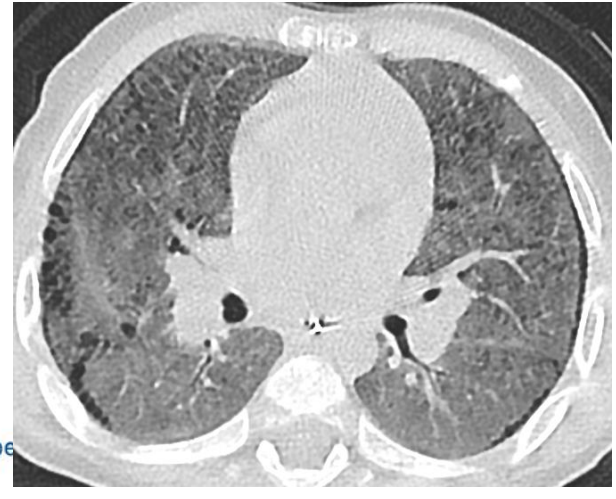
Nathan et al. Eur Respir Rev 2023

CASE 1 (M.)
Treatment and follow-up

- IV corticosteroid pulses
- Azithromycin
- Hydroxychloroquine
- NIV => oxygen support
- Enteral nutrition
- Immunizations



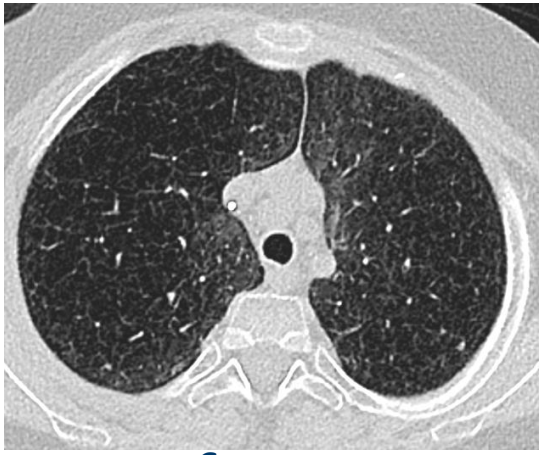
14 months



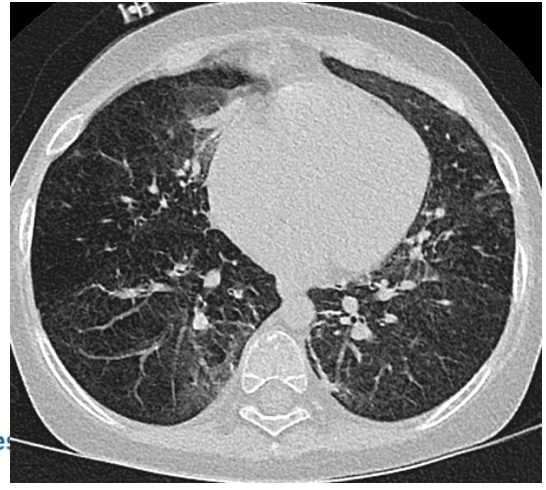
CASE 1 (M.)
Treatment and follow-up

- IV corticosteroid pulses … 84
- Azithromycin … ongoing
- Hydroxychloroquine … stop because of retinitis
- NIV => oxygen support … ongoing + NIV 20h/24
- Enteral nutrition … ongoing
- Immunizations

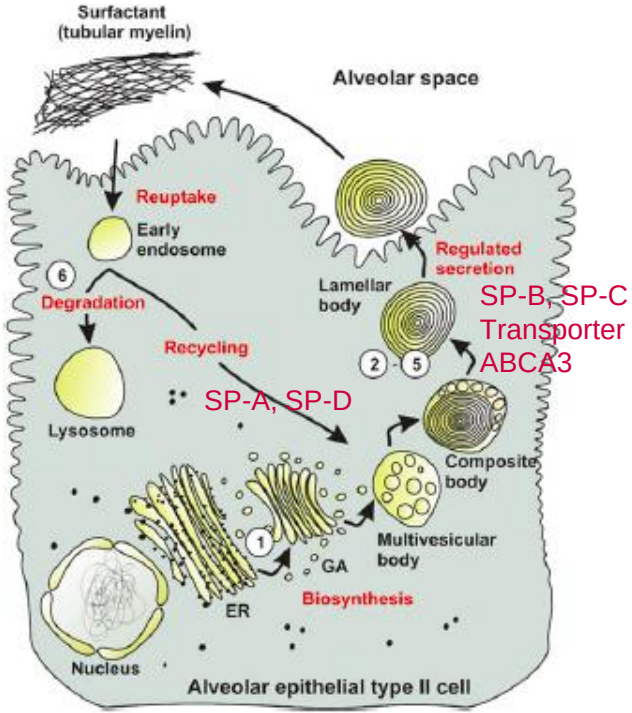
- Waiting list for lung transplantation at 4 years and 9 months (duration 1 year and 5 months)
- Death at 6 years and 2 months (O neg)



6 years



Surfactant disorders



4 surfactant proteins
- SP-A, SP-B, SP-C, SP-D

Genes *SFTPA1, SFTPA2, SFTPB, SFTPC, SFTPB*

Transporter into lamellar bodies: ABCA3

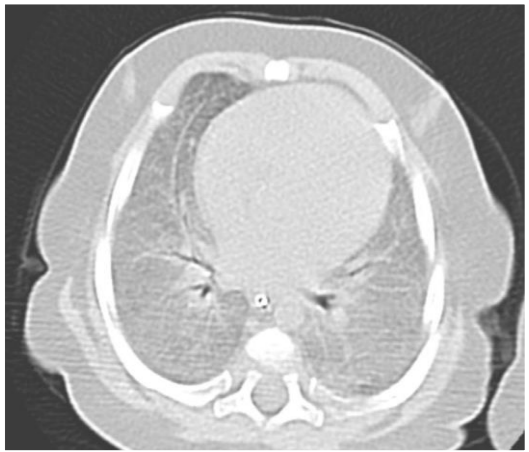
Transcription factor: NKX2.1

Most severe forms: SP-B and ABCA3 mutations

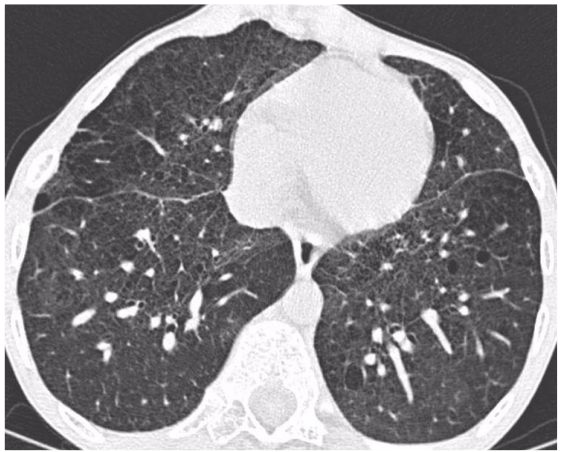
Schindlbeck U, et al. Hum Mutat. 2018

ABCA3 (*ABCA3*) mutations: typical forms

- Phospholipid transporter, ATP binding cassette family
- **Inheritence**: recessive
- **Phenotype**:
  - Neonatal or infant respiratory distress
  - Failure to thrive
  - Evolution towards death or severe ILD with fibrosis



3 months

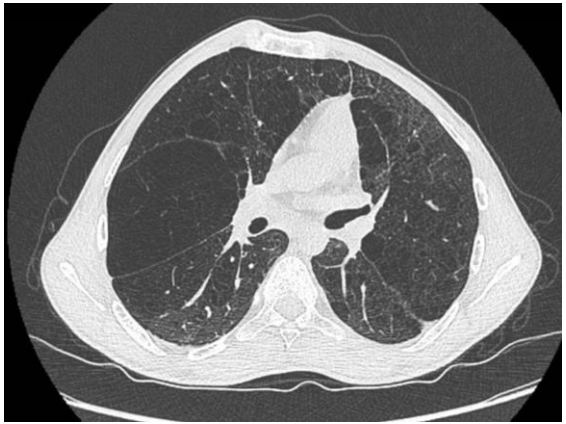


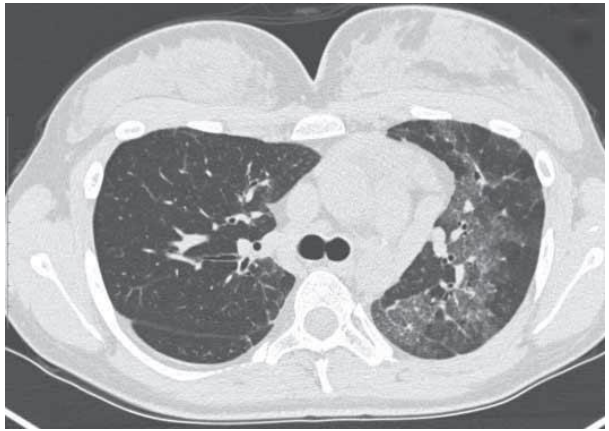
15 years

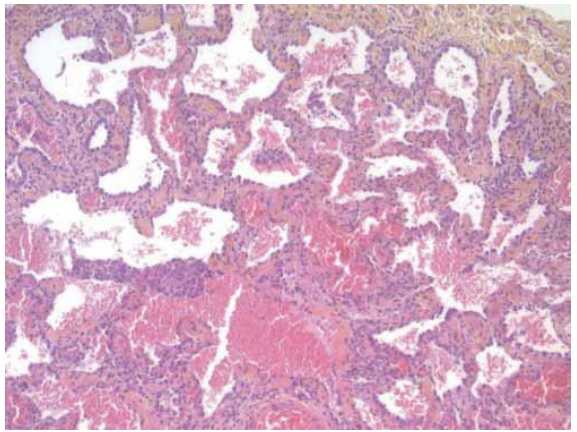
Doan ML et al. Thorax 2008
Whitsett et al. Annu Rev Med. 2010

ABCA3 (*ABCA3*) mutations: typical forms

Adult evolution and/or adult onset
Lung fibrosis in adults: « combined emphysema and fibrosis »



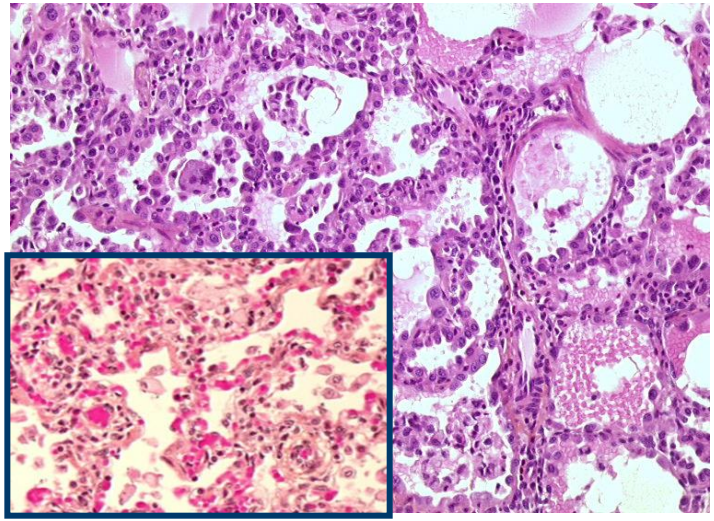




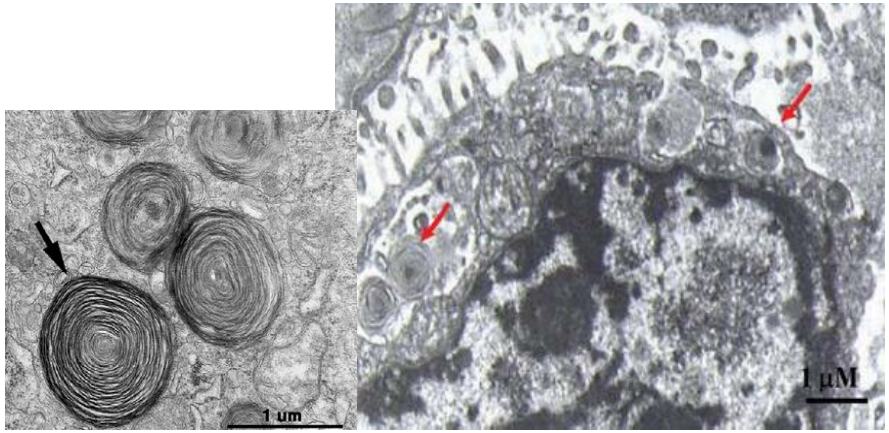
Manali et al. ERJ open research 2019

ABCA3 (*ABCA3*) mutations: typical forms

- Enlarged alveolar walls
- Alveolar epithelial cells hyperplasia
- Alveolar proteinosis
- EM: dense inclusions in abnormal and small lamellar bodies



Control *ABCA3* mutant



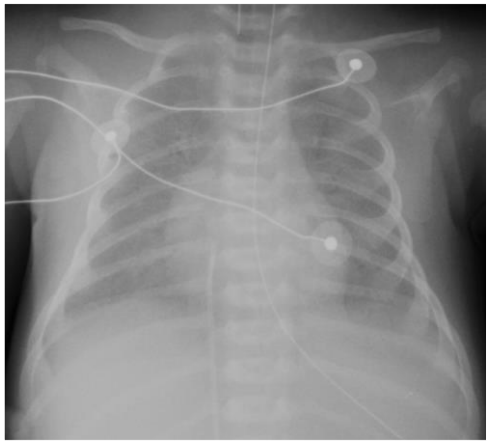
Control *ABCA3* mutant

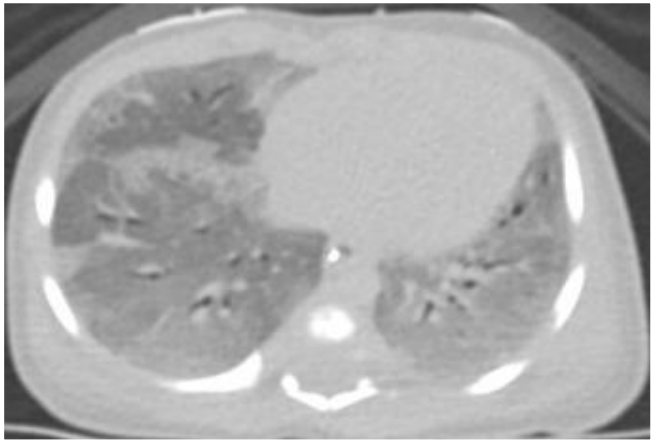
Gower et al. *J pediatr* 2010
Flamein et al. *Hum Mol Genetics* 2011
Shulenin et al. *NEJM* 2004

SP-B (*SFTPB*) mutations

Typical form

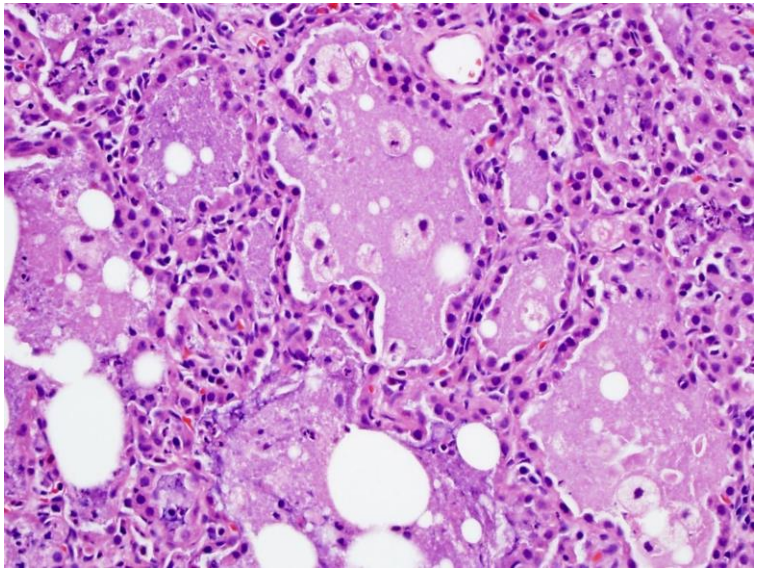
- **Transmission** : recessive
- **Phenotype** :
  - Severe neonatal respiratory distress
  - Pulmonary hypertension
  - Refractory hypoxemia
  - Lethal prognosis



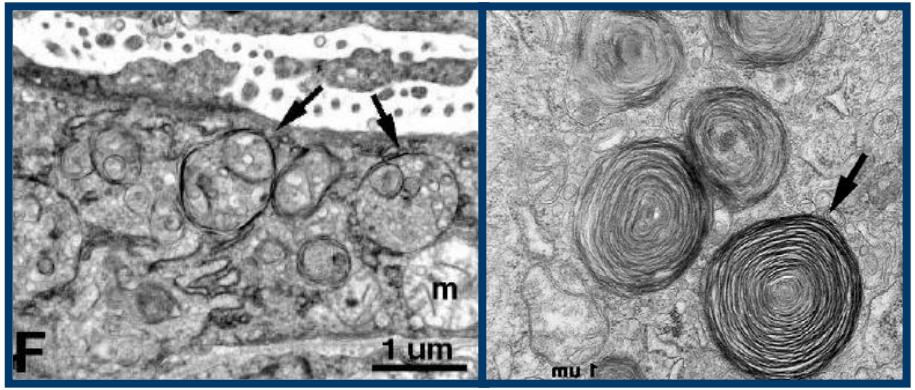


Nogee et al.NEJM 1994
Doan ML et al. Thorax 2008
Images: Radiology department, Trousseau hospital

SP-B (*SFTPB*) mutations



- Alveolar proteinosis
- Thick and stiff alveolar walls
- AEC2 hyperplasia



SFTPB mutant

SFTPB WT

Vanishing lamellar bodies

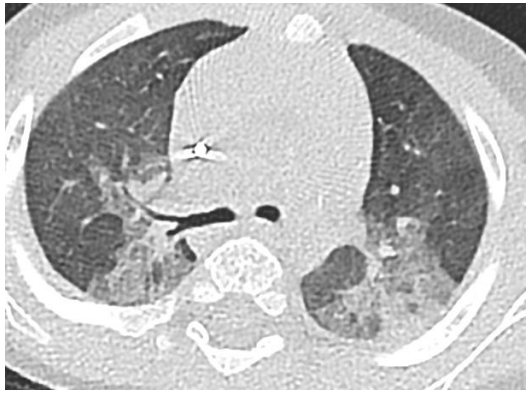
Nogee et al. NEJM 1994
Wert et al. Ped and Dev Pathology 2010

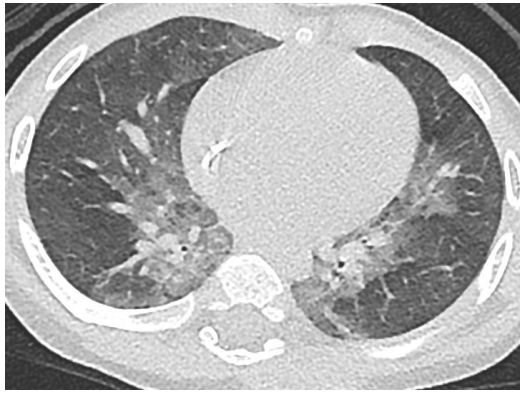
TTF1 (*NKX2.1*) mutations

Transcription factor for
- Brain
- Thyroid (thyroglobulin)
- Lungs (SP-B, SP-C, ABCA3)

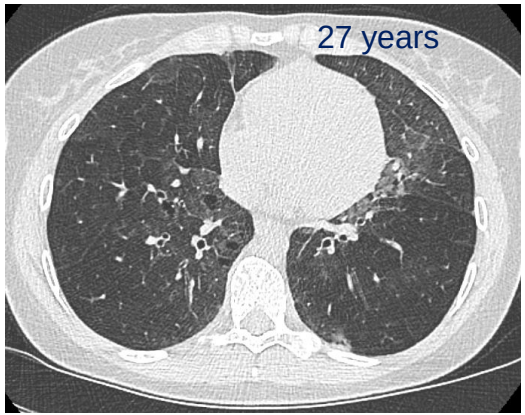
Typical forms

- Heterogeneous from birth to adulthood presentation
- Transmission : dominant
- Phenotype : “brain-lung-thyroid” syndrome with various degrees of
  - Hypotonia / Benign chorea
  - ILD / lung fibrosis
  - Hypothyroidism





16 months



Jovien S et al. Respiration 2016
Nattes et al. Respir Med 2017

Neonatal respiratory distress
When to suspect a surfactant disorder?

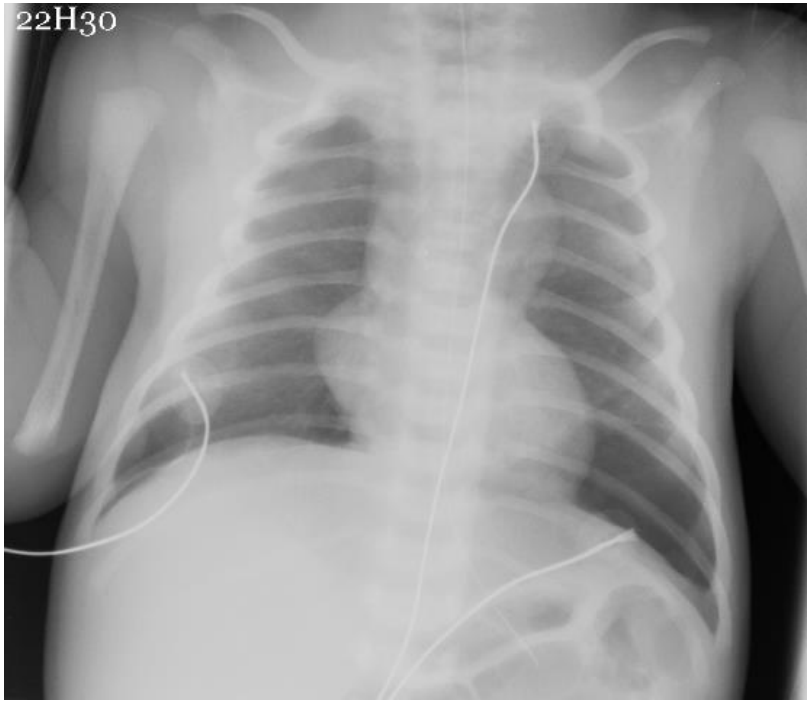
- Term newborn
- Consanguinity (SP-B, ABCA3)
- No extra-respiratory disease (SP-B, ABCA3)
- OR peripheral hypothyroidism / hypotonia (NKX2.1)
- Moderate to severe PHT
- Diffuse GGO
- Transient efficacy of exogeneous surfactant

CASE 2 (L.)

- First child
- Unremarkable pregnancy
- No consanguinity

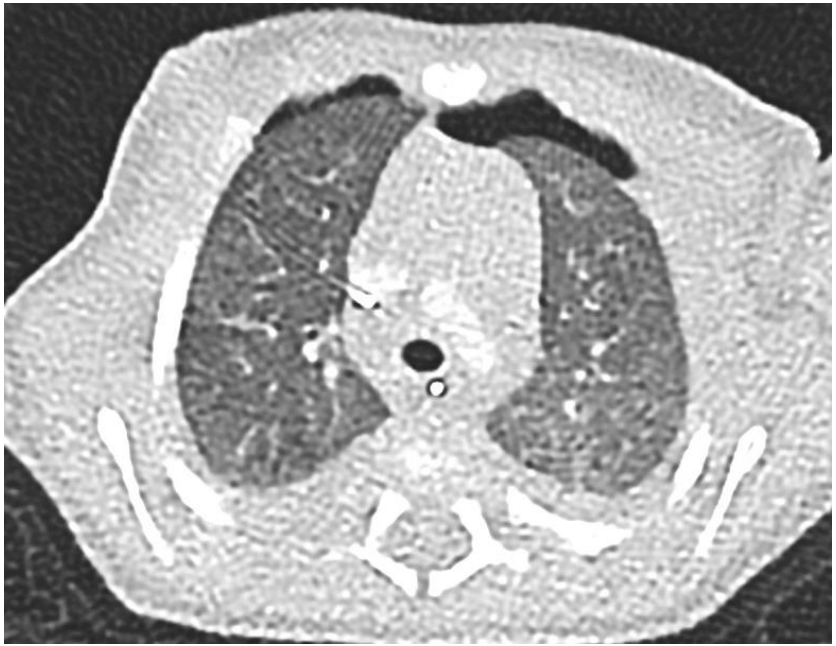
- Full-term newborn
- Immediate NRD
- Severe PHT
- Refractory hypoxaemia => ECMO

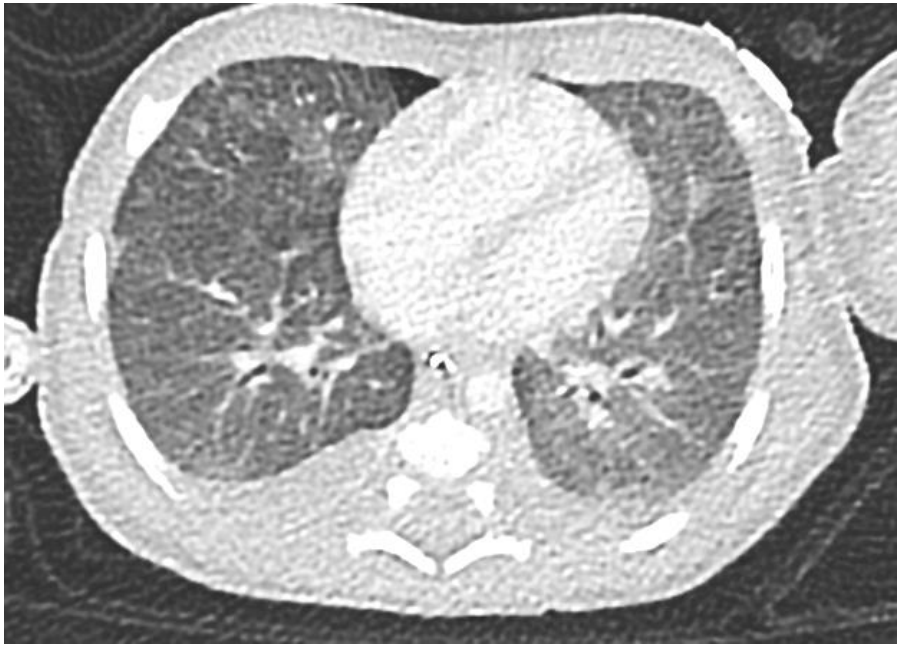
- Duodenal atresia



CASE 2 (L.)

HRCT at 14 days





Neonatal interstitial lung disease: which one? (MCQ)

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B. Brain-lung-thyroid syndrome (NKX2.1)
C. Pulmonary interstitial glycogenosis
D. Alveolar capillary dysplasia
E. Acinar dysplasia

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Nathan et al. Expert Rev Respir Med 2018

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Pros: Neonatal onset

Cons: No consanguinity (SP-B, ABCA3)
No hypothyroidism
Severe PHT
CT pattern
Extra-respiratory disorder

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Extra-respiratory disorder

Pros: Neonatal onset

Cons: No congenital heart disease

Pros: Neonatal onset
Severe PHT
Sub-normal CT-scan
Digestive extra-respiratory disorder

Cons:

Which investigation could confirm the diagnosis? (MCQ)

A. Lung biopsy
B. Caryotype
C. Bronchoalveolar lavage
D. Echocardiography
E. NGS molecular testing

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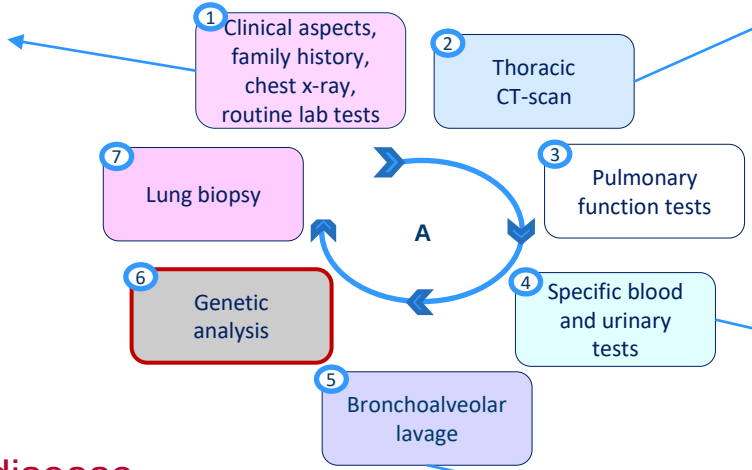
Diagnostic workup in chILD



Digestive and lung disease

Sub-normal

No thyroid disorder
No metabolic disorder

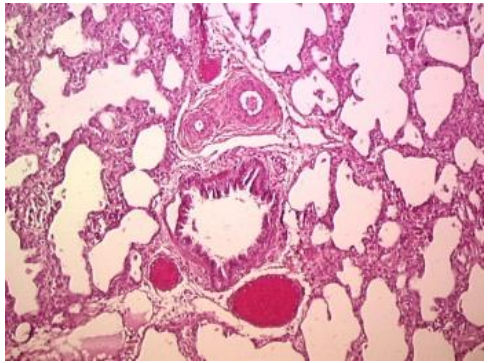
Severe lung disease
Biopsy / genetic testing?
Both +++

Unstable => not performed

Nathan et al. Eur Respir Rev 2023

Diagnostic workup in chILD

Digestive and lung disease



1 Clinical aspects, family history, chest x-ray, routine lab tests

2 Thoracic CT-scan

Sub-normal

3 Pulmonary function tests

4 Specific blood and urinary tests

No thyroid disorder
No metabolic disorder

5 Bronchoalveolar lavage

Unstable => not performed

6 Genetic analysis

7 Lung biopsy

A

NGS panel for surfactant and PHT disorders
Heterozygous *FOXF1* mutation

Nathan et al. Eur Respir Rev 2023

CASE 2 (L.)
Alveolar capillary dysplasia
(with misalignment of pulmonary veins)

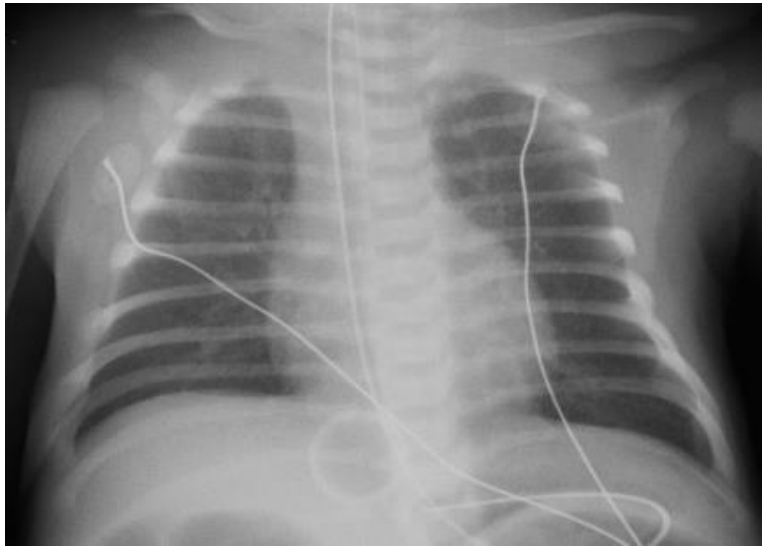
- **Diffuse developmental disorder**

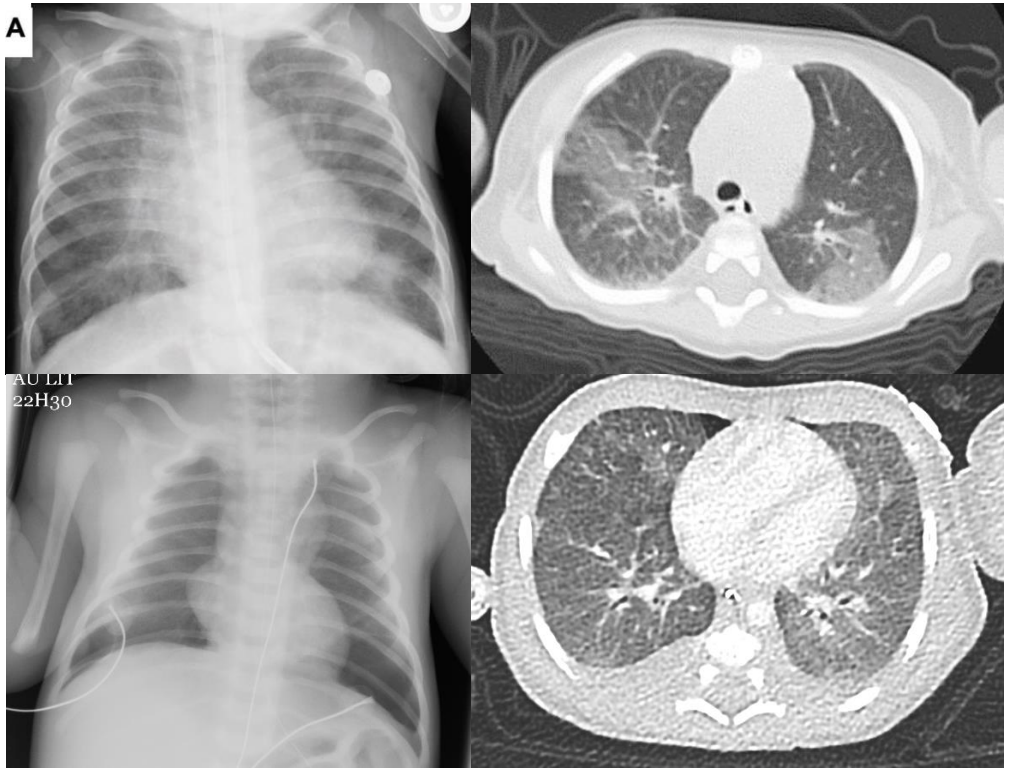
Vascular and alveolar abnormalities, poor capillary bed
Abnormal localization of pulmonary veins in the broncho-arterial axix, thickened alveolar walls

- **Typical forms**
  - Full-term newborn
  - Severe PHT (90%) with refractory hypoxemia (60%)
  - Extra-exrespiratory malformations (50-80%)
    - Heart
    - Intestine (rotation abnormalities ++)
    - Uro-genitary
- **Evolution: Most cases are fatal**

Bishop NB et al. *Am J Respir Crit Care Med*. 2011
Slot E et al. *Pulm Circ.* 2018
Szafranski P et al. *Am J Hum Genet*. 2014
Pasutto F et al. *Am J Hum Genet.* 2007

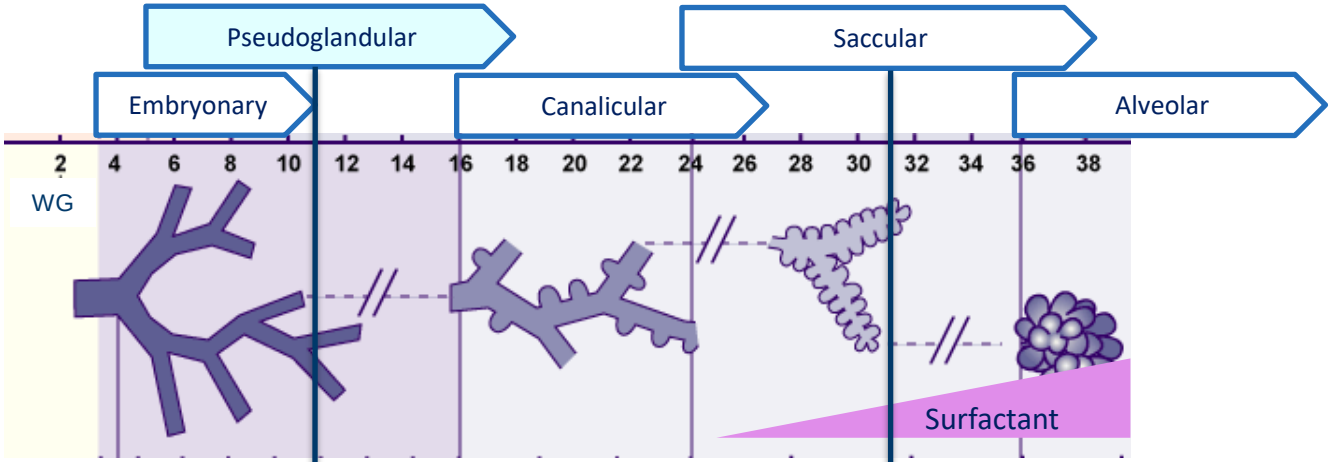
CASE 2 (L.)
Alveolar capillary dysplasia
(with misalignment of pulmonary veins)

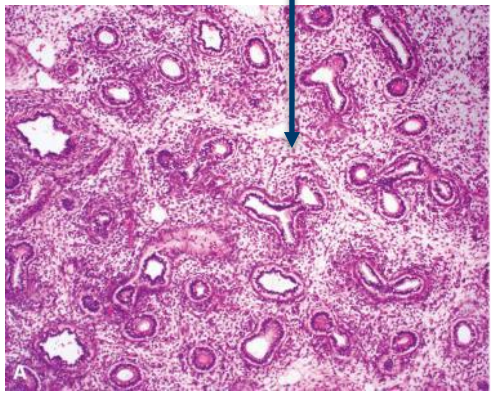




Ito et al. *Eur J Pediatr*. 2015
Szafranski P et al. *Am J Hum Genet*. 2014
Radiology department, Trousseau hospital

Other developmental disorders of the lung





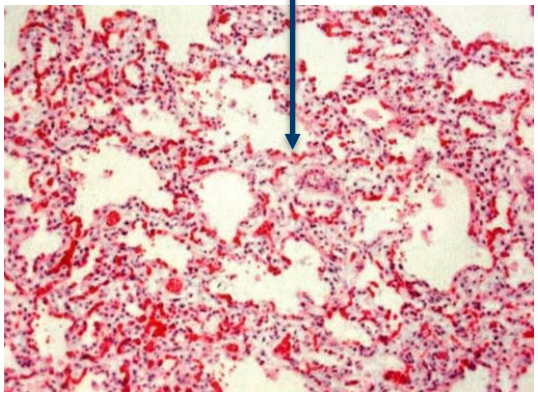
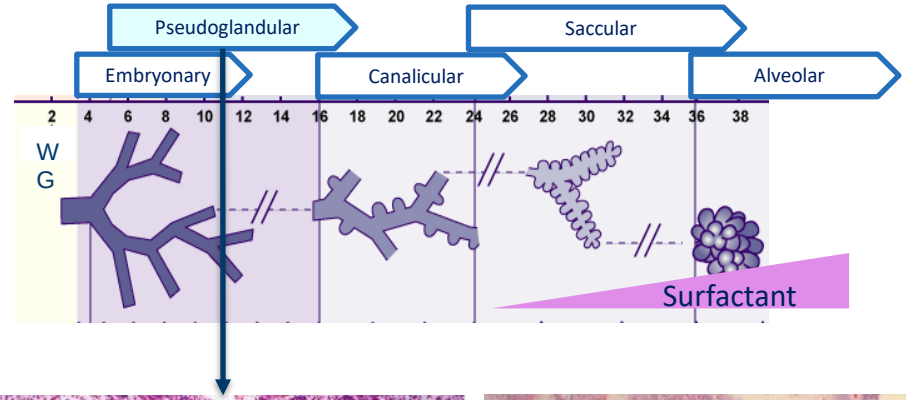
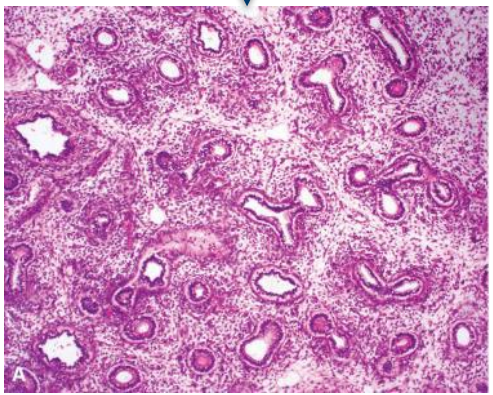
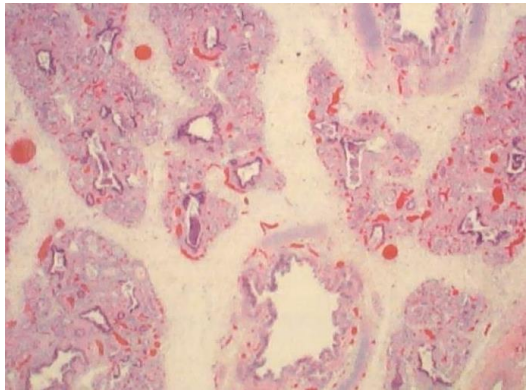


Image: Pr. Megan Dishop

Acinar dysplasia







Early arrest of development at the pseudoglandular stage

- Airways present but no alveolus
- Low developed capillary bed

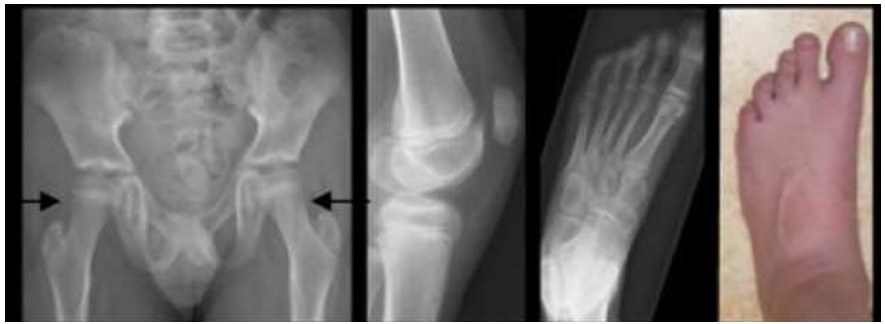
6F/1M
Extra-respiratory disorders: renal dysplasia, right aorta arch, cerebral and adrenal bleedings or calcifications

Szafranski P et al. *Am J Med Genet*. 2016

Syndromic acinar dysplasia

***TBX4*: Small patella syndrome + acinar dysplasia**

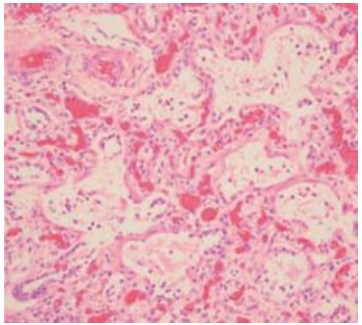
- Bone malformations, mainly hips, legs, feets
- Heterogeneous acinar dysplasia with PHT at the forefront



Szafranski P et al. *Am J Med Genet*. 2016
Kerstjens-Frederikse WS et al. *J Med Genet.* 2013

***FGFR2*: Ectrodactily + acinar dysplasia**

- Only one report
- Neonatal severe PHT



Barnett CP et al. *Hum Mutat*. 2016

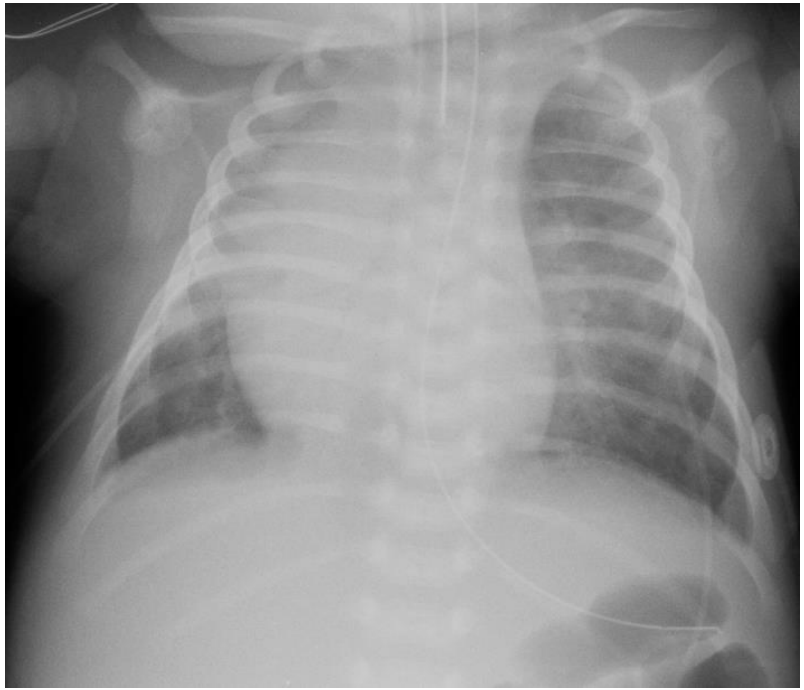
Neonatal respiratory distress
When to suspect a diffuse developmental disorder of the lung?

- Term newborn
- Severe PHT
- Extra-respiratory malformations
- No impact of exogeneous surfactant
- Sub-normal / heterogeneous CT-scan

CASE 3 (A.)

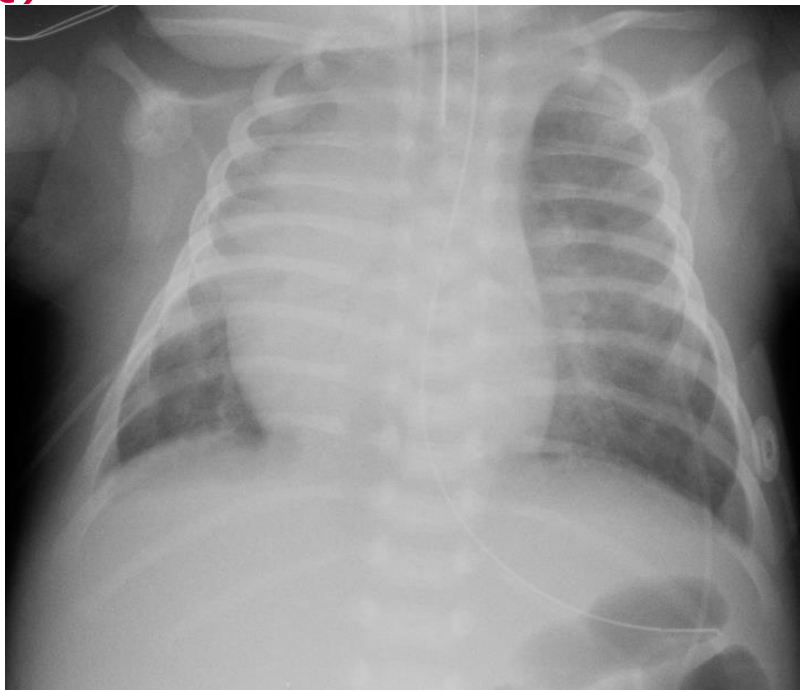
- First child
- Unremarkable pregnancy
- Consanguinity

- Full-term newborn
- Immediate moderate NRD
- No PHT



What can you describe on the chest X-ray? (MCQ)

A. The chest x-ray is in oblique projection
B. Thicken bronchial walls with alveolar opacities
C. Cardiomegaly
D. Enlarged thymus
E. Interstitial opacities



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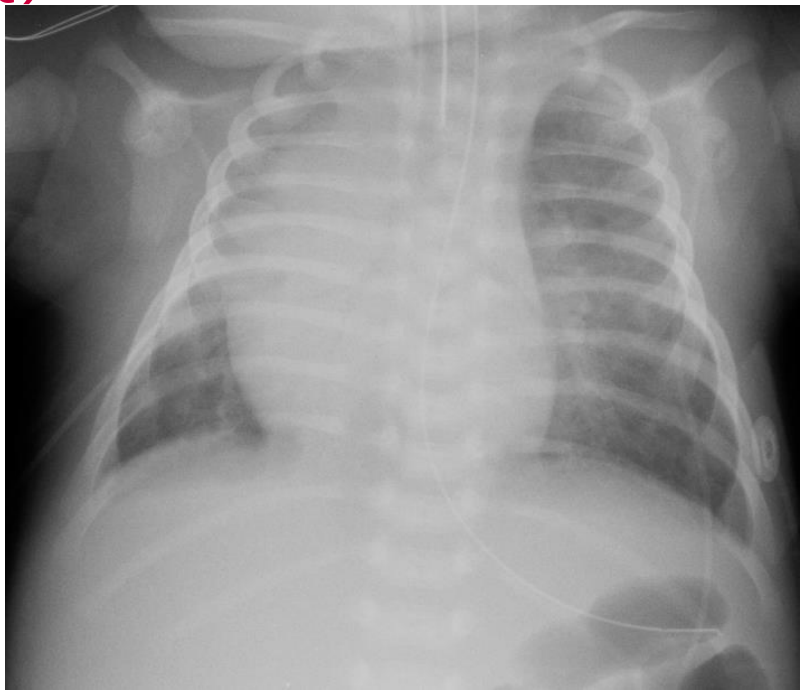


CASE 3 (A.)

- Situs inversus
- Neonatal rhinitis

⇒ PCD suspicion

⇒ Genetic test
⇒ Nasal/bronchial biopsy for ciliary EM

Lucas JS, et al. Eur Respir J. 2017

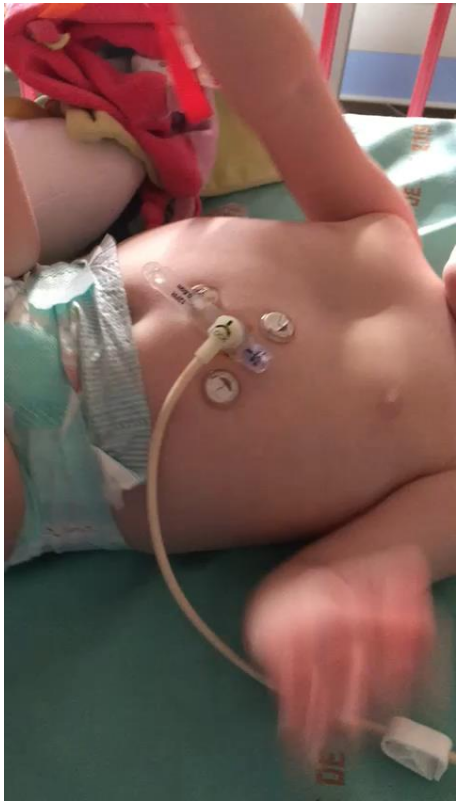
Neonatal respiratory distress
When to suspect an ILD differential dagnosis?

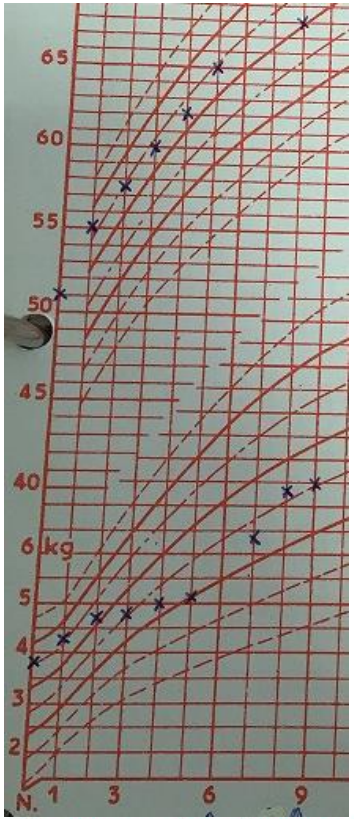
- **Primary ciliary dyskinesia?**
  - Consanguinity
  - Neonatal rhinitis
  - Situs inversus
- **Cystic fibrosis?**
  - Consanguinity
  - Meconial ileus
- **Congenital heart disease?**
  - Cardiomegaly
  - Signs of cardiac insufficiency

CASE 4 (S.)

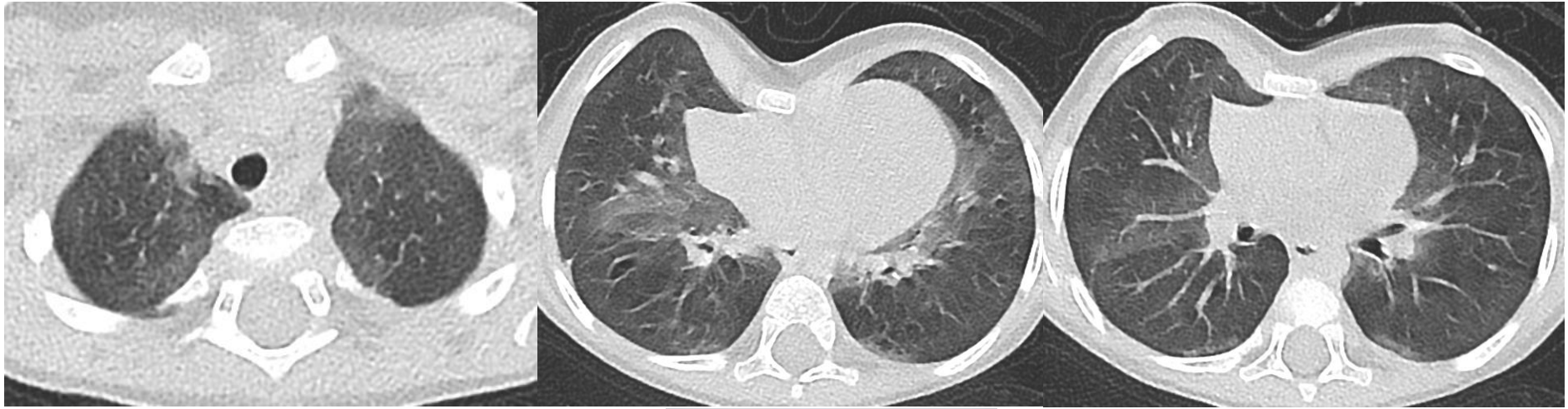
- 2nd child, full-term newborn, no neonatal respiratory distress
- Well being until 4 months
- No severe infection
- Persistent tachypnea observed since the age of 4 months
  - Retractions
  - Persitent crackles
  - Pectus excavatum
  - Oxygen therapy at 4 months
- Growth impairement requiring enteral nutrition at 7 months

- Biology: No abnormality





CASE 4 (S.)
Radiologic diagnosis



Childhood interstitial lung disease: which one? (MCQ)

A. Immune deficiency (oportunistic infection)
B. Brain-lung-thyroid syndrome (NKX2.1)
C. Neuroendocrine cell hyperplasia of infancy
D. SP-C disorder
E. Alveolar haemorrhage

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C. Neuroendocrine cell hyperplasia of infancy
D. SP-C disorder
E. Alveolar haemorrhage

2010 & 2018 childhood ILD (chILD) classification

ILD related to exposure/environment insults	ILD related to systemic diseases processes	ILD related to lung primary parenchyma dysfunctions	ILD specific to infancy
Hypersensitivity pneumonitis	Connective tissue diseases	Surfactant disorders	Neuroendocrine cell hyperplasia of infancy
Medication, Drugs	Vasculitis	Diffuse alveolar hemorrhages	Pulmonary interstitial glycogenosis
Radiation exposure	Granulomatous disorders	Eosinophilic lung diseases	Diffuse developmental disorders
	Metabolic disorders	Lymphatic disorders	
		Viral infections	

Pros: Always possible … SP-C? NKX2.1?

Cons: No consanguinity (SP-B, ABCA3)
No hypothyroidism, no hypotonia
CT pattern

Pros:

Cons: Delayed onset
No PHT
CT pattern
No extra-respiratory disorder

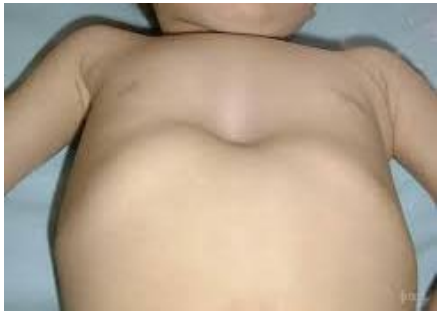
Pros: Age at onset
CT pattern
« well-being child »
Liptzin score

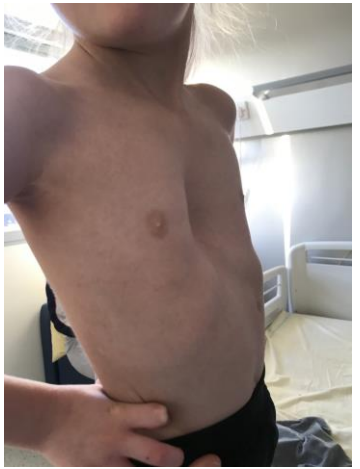
Cons:

Liptzin score for NEHI / PTI

NEHI score (0 to 10)

Criteria	**Present = 1, Absent = 0**
Onset before 12 months	
Failure to thrive	
No clubbing	
No basline cough	
No baseline wheezing	
Chest wall abnormality (ex: pectus excavatum)	
Crackles	
Hypoxemia	
Tachypnea	
Retractions	
TOTAL (≥7 highly suggestive of NEHI)	



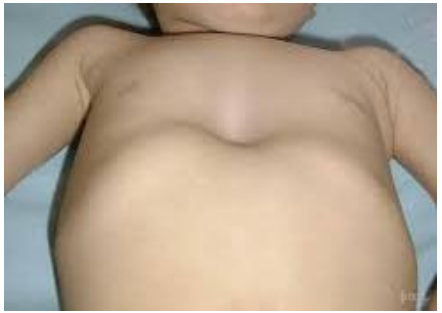


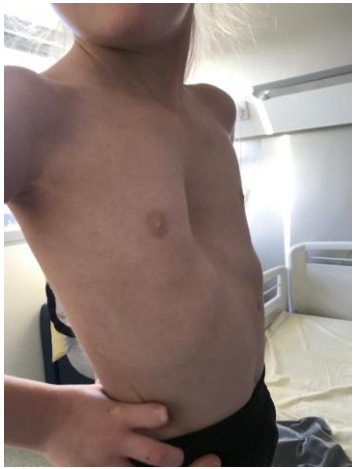
Liptzin D et al. Ann ATS 2020

Liptzin score for neuroendocrine cell hyperplasia of infancy (NEHI) / persistent tachypnea of infancy (PTI)

NEHI score (0 to 10)

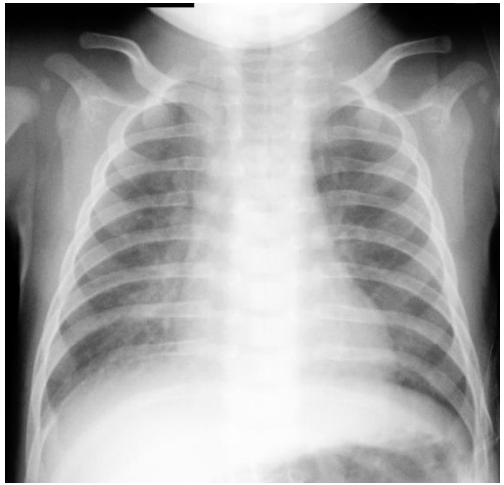
Criteria	**Present = 1, Absent = 0**
Onset before 12 months	1
Failure to thrive	1
No clubbing	1
No basline cough	1
No baseline wheezing	1
Chest wall abnormality (ex: pectus excavatum)	1
Crackles	1
Hypoxemia	1
Tachypnea	1
Retractions	1
TOTAL (≥7 highly suggestive of NEHI)	**10**



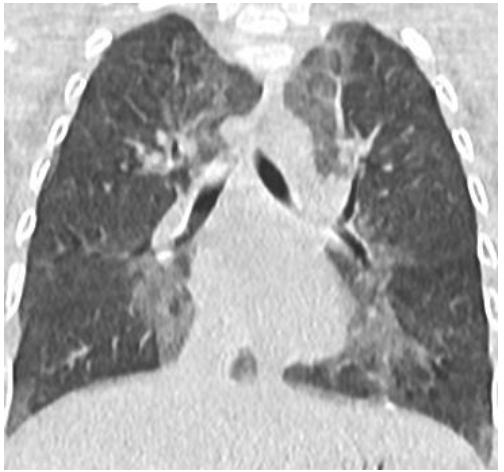


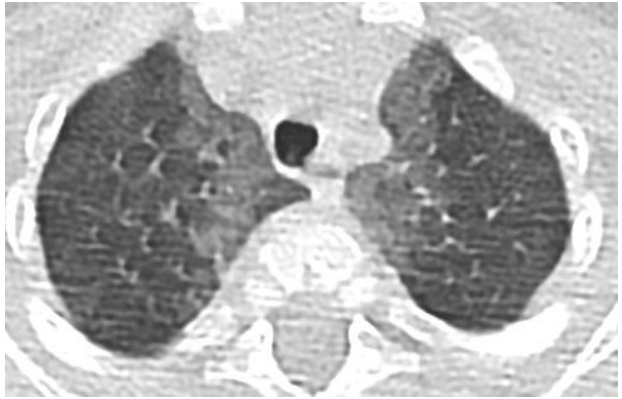
Liptzin D et al. Ann ATS 2020

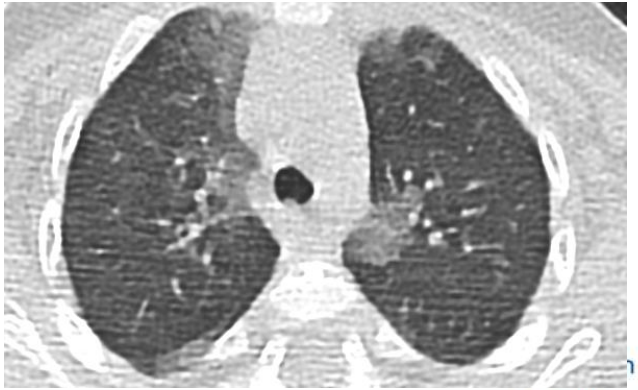
Another patient same diagnosis

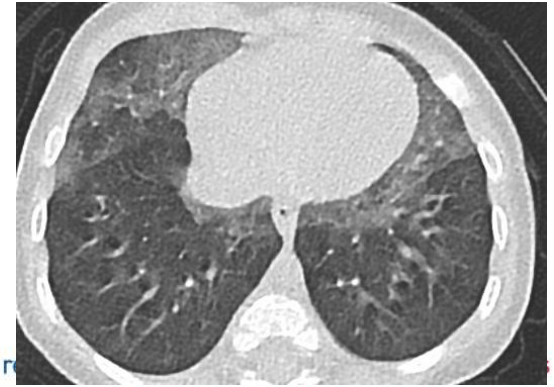


3 months



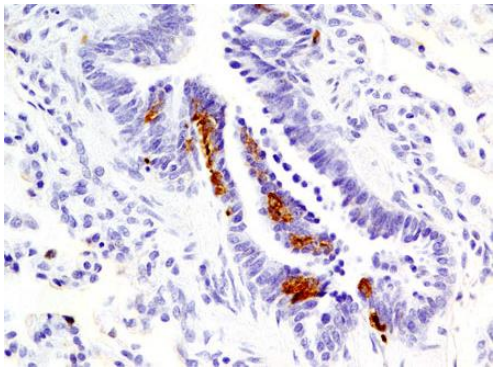


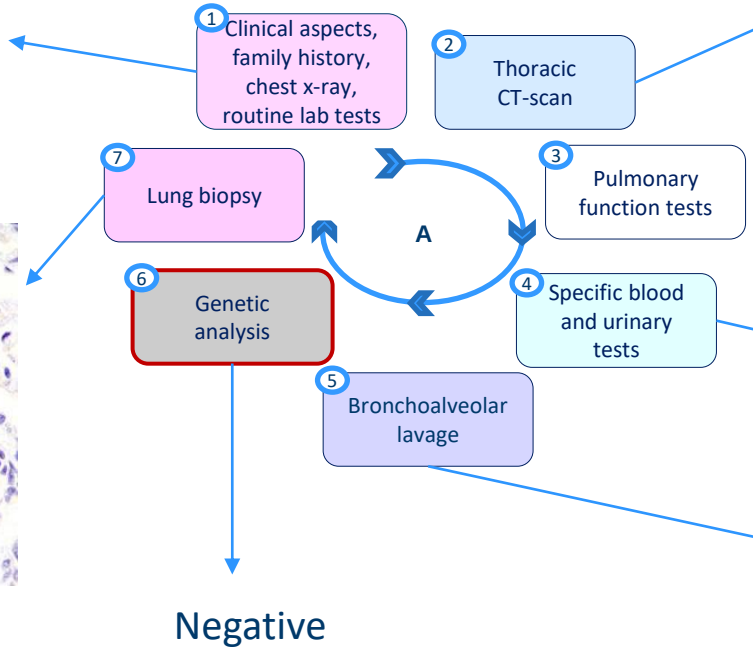




Diagnostic workup in chILD

Liptzin score +





Typical of NEHI

No thyroid disorder
No metabolic disorder

Normal

Negative

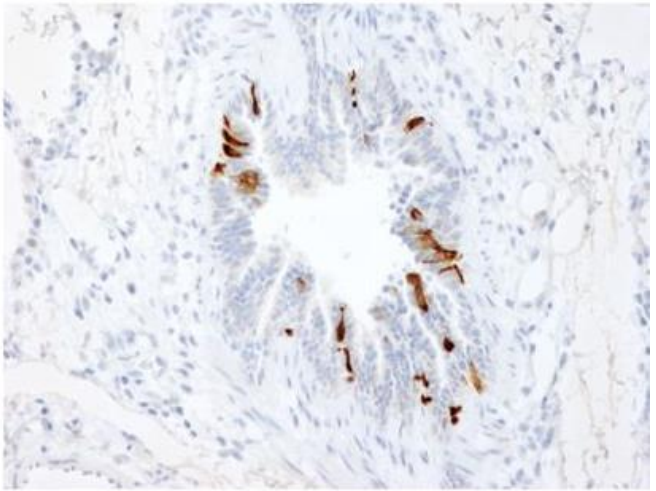
Nathan et al. Eur Respir Rev 2023

PTI / NEHI

- NEHI: high number of NE cells in the distal bronchioles
- Diagnosis: lung biopsy with bombesin staining

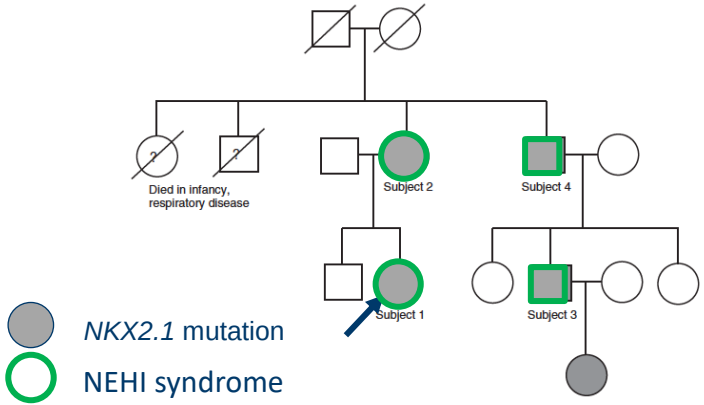
- IV corticosteroid pulses (or no treatment?)

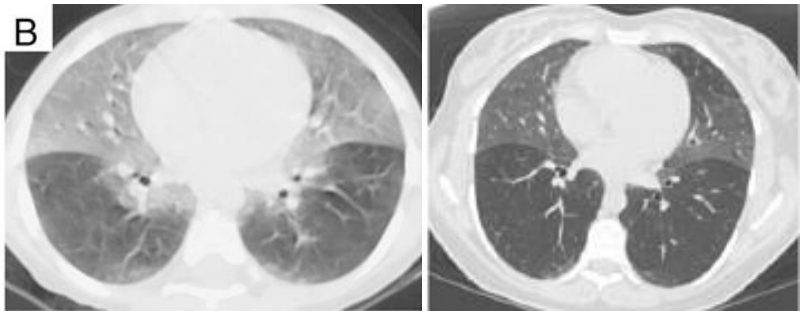
- Evolution: good!
  - Weaned from oxygen at 2,5 years
  - Weaned from EN at 3 years



Devaux et al. Eur J Ped 2022
Fabre et al. Eur J Ped 2022

PTI / NEHI: a genetic cause?





3 ans 26 ans

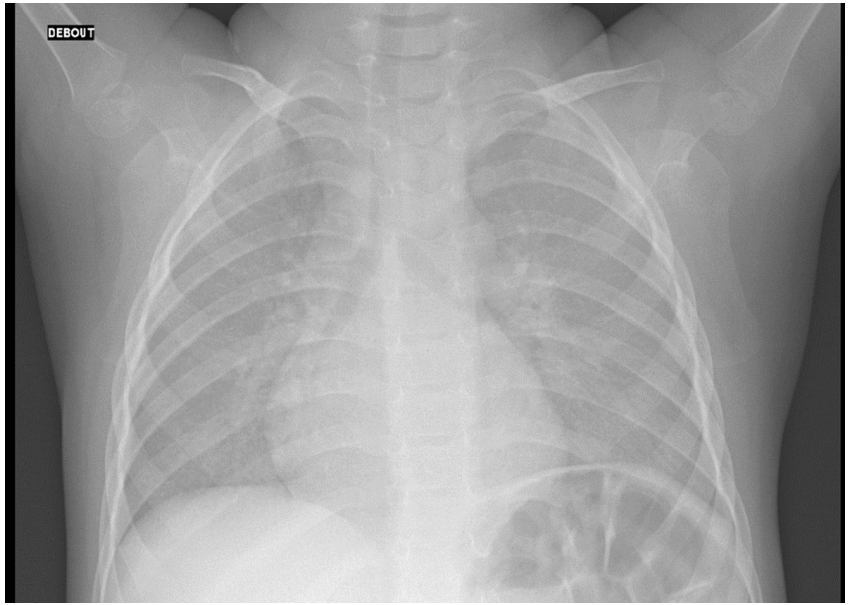
Young et al. Chest 2013
Nevel et al. Ann Am Thorac Soc 2016
Jiramethee et al. Case Rep Pulmonol 2017

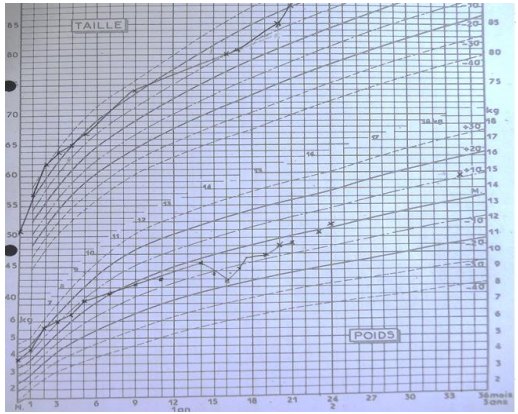
ILD in childhood
When to suspect a NEHI?

- Liptzin score + CT-scan pattern
- Negative genetic tests for surfactant genes

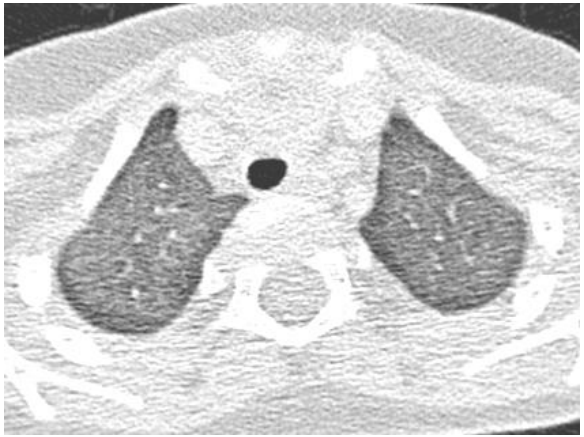
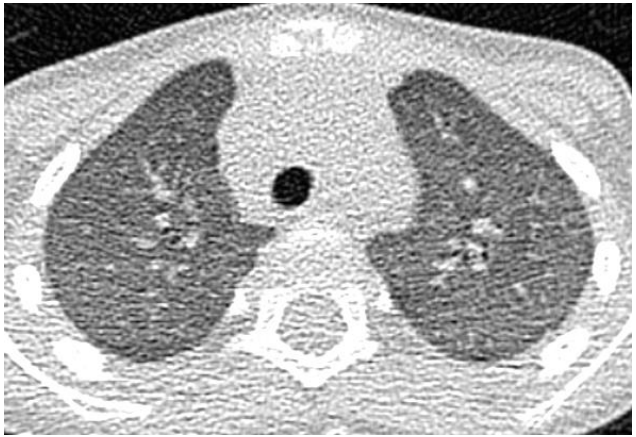
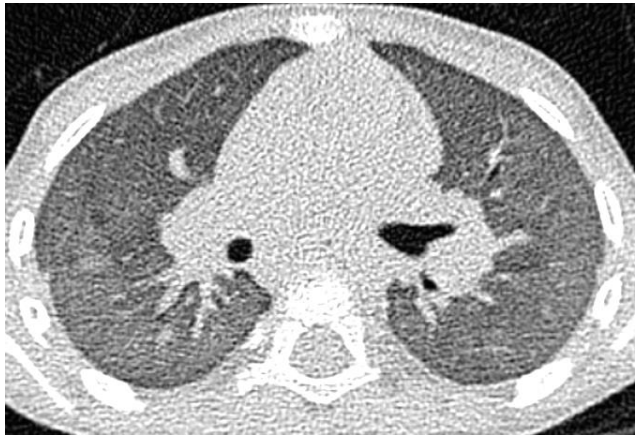
CASE 5 (J.)

- 2nd child, full-term newborn, no neonatal respiratory distress
- Well being until 18 months … BUT growth impairement since the age of 7 months
- RSV bronchiolitis at 18 months with oxygen requirement … persisting with crackles and unusual chest X-ray





CASE 5 (J.)

18 months

Childhood interstitial lung disease: which one? (MCQ)

A. Immune deficiency (oportunistic infection)
B. Brain-lung-thyroid syndrome (NKX2.1)
C. Neuroendocrine cell hyperplasia of infancy
D. SP-C disorder
E. Alveolar haemorrhage

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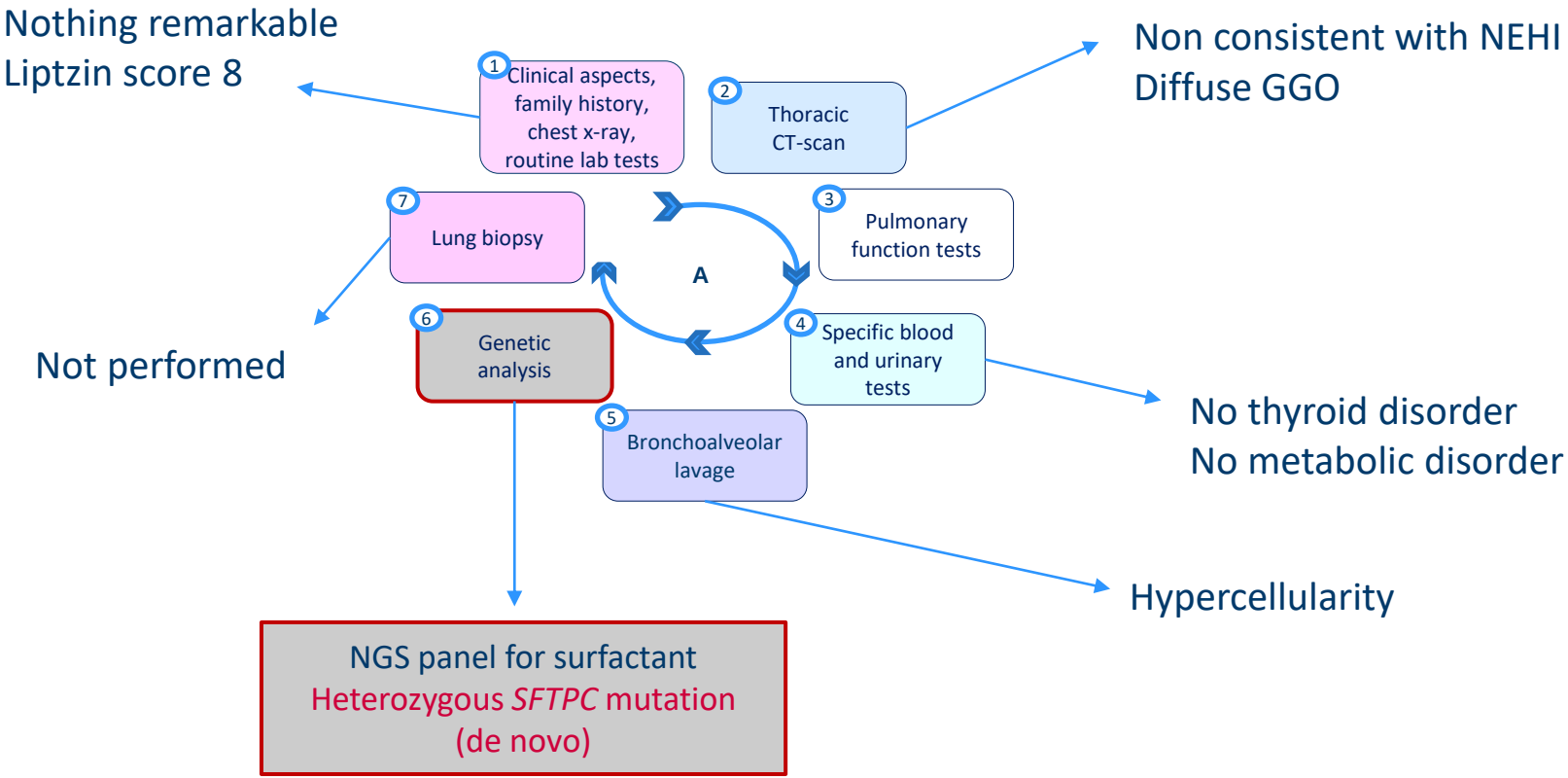
Diagnostic workup in chILD



Nathan et al. Eur Respir Rev 2023

CASE 5 (J.): Evolution

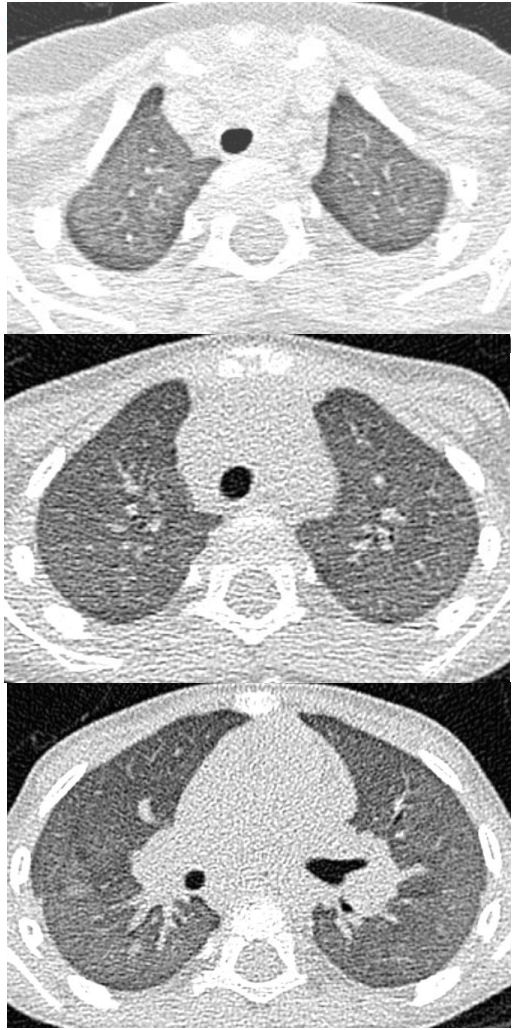
- Oxygen therapy for 2 years
- No enteral nutrition
- IV methylprednisolone pulses … 10
- Azithromycin … still
- Hydroxychloroquine … still

Stable over time with preserved activities

Meals are still an issue

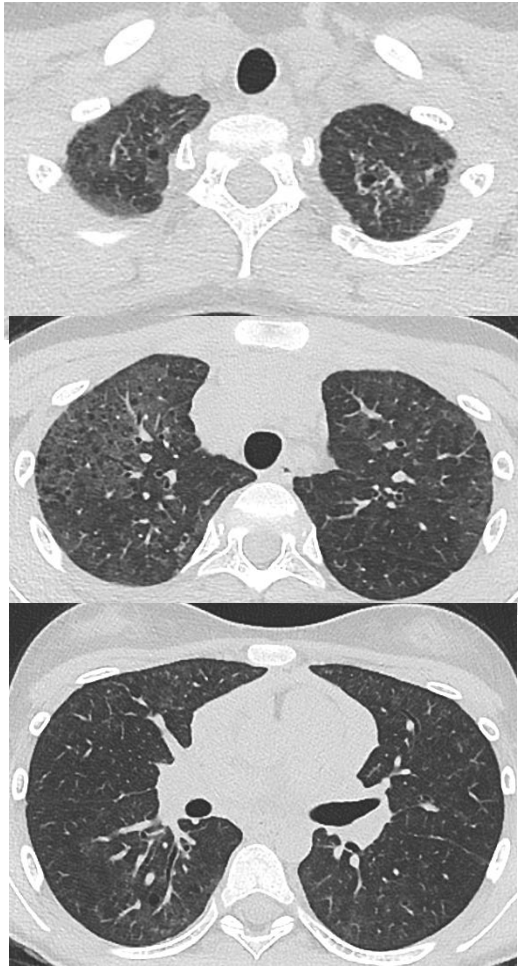
Current lung function: FVC 43%, DLCO 44%

CASE 5 (J.)



18 months

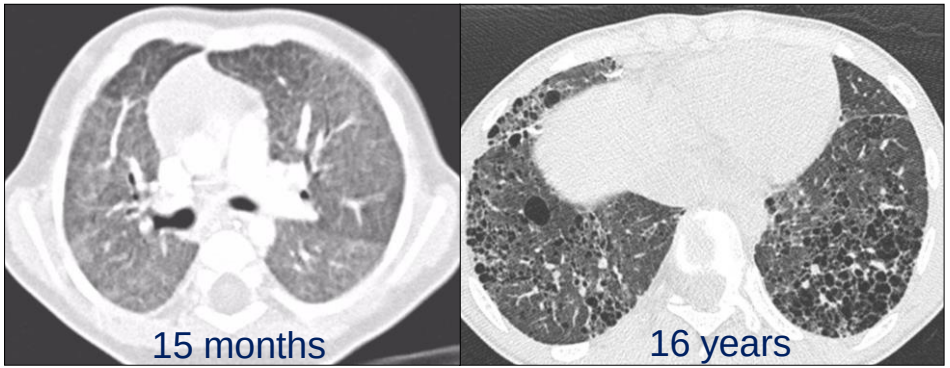
10 years

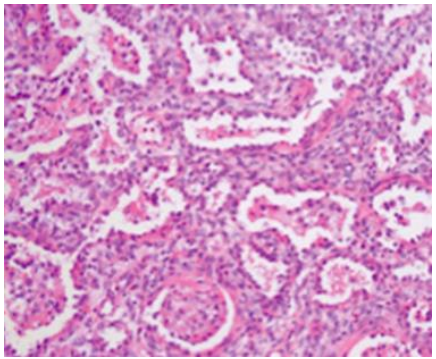


SP-C (SFTPC) Mutations

Typical forms

- **Transmission**: Dominant inheritance
- **Phenotype**:
  - Neonatal or infant respiratory distress, often following a viral infection
  - Failure to thrive
  - Evolution towards severe fibrosing ILD





Doan ML et al. Thorax 2008
Whitsett et al. Annu Rev Med. 2010

ILD in childhood
When to suspect a SP-C disorder?

- Phenotypic heterogeneity

- Early onset
- Following a viral infection

- Diffuse GGO on CT-scan

Take home messages

chILD diagnostic assessment based on CT-scan pattern before 2 years

Diffuse and dense GGO	
Diffuse and ± dense GGO peripheral and/or parenchymal traction cysts, traction bronchiectasis, reticulations	
Paramediastinal, paracardial, middle lobe, lingula GGO	
Sub-normal	

Take home messages

chILD diagnostic assessment based on CT-scan pattern before 2 years

Diffuse and dense GGO	Surfactant disorder
Diffuse and ± dense GGO peripheral and/or parenchymal traction cysts, traction bronchiectasis, reticulations	
Paramediastinal, paracardial, middle lobe, lingula GGO	
Sub-normal	

Take home messages

chILD diagnostic assessment based on CT-scan pattern before 2 years

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Sub-normal	

Take home messages

chILD diagnostic assessment based on CT-scan pattern before 2 years

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Diffuse and ± dense GGO peripheral and/or parenchymal traction cysts, traction bronchiectasis, reticulations	Surfactant disorder
Paramediastinal, paracardial, middle lobe, lingula GGO	NEHI, PTI
Sub-normal	

Take home messages

chILD diagnostic assessment based on CT-scan pattern before 2 years

Diffuse and dense GGO	Surfactant disorder
Diffuse and ± dense GGO peripheral and/or parenchymal traction cysts, traction bronchiectasis, reticulations	Surfactant disorder
Paramediastinal, paracardial, middle lobe, lingula GGO	NEHI, PTI
Sub-normal	Diffuse developmental disorder of the lung

Take home messages

Stepwise approach to chILD diagnosis

Workup step 1

Who	General Paediatrician Suspect ILD
Investigations	Clinical evaluation and family history
	Chest x-ray Lab and urine routine tests
Diagnosis	ILD suspicion

Nathan et al. *Eur Respir Rev* 2023

	Workup step 1	Workup step 2
Who	**General Paediatrician** Suspect ILD	**Paediatric pulmonologist** / **Expert centre** Confirm ILD, eliminate differential diagnosis, classify disease
Investigations	Clinical evaluation and family history Chest x-ray Lab and urine routine tests	Serological and other blood tests, pulmonary function tests (age dependent) HR thoracic CT-scan Bronchoscopy, BAL Genetic tests Lung biopsy (or biopsy of other targeted organ)
Diagnosis	**ILD suspicion**	

Nathan et al. *Eur Respir Rev* 2023

Who	Workup step 1	Workup step 2
	General Paediatrician Suspect ILD	**Paediatric pulmonologist / Expert centre** Confirm ILD, eliminate differential diagnosis, classify disease
Investigations	Clinical evaluation and family history	Serological and other blood tests, pulmonary function tests (age dependent)
	Chest x-ray Lab and urine routine tests	HR thoracic CT-scan Bronchoscopy, BAL
		Genetic tests Lung biopsy (or biopsy of other targeted organ)
Diagnosis	**ILD suspicion**	**Confirmed ILD diagnosis**

With CT, specific lab tests, BAL
- PTI
- Exposure-related ILD
- Hypersensitivity pneumonitis
- DAH
- Systemic / auto-immune disease
- Metabolic disorder

With molecular genetics
- Surfactant disorder
- Pulmonary alveolar proteinosis
- Autoinflammatory disorders

With lung biopsy
- NEHI
- Pulmonary interstitial glycogenosis
- Sarcoidosis

With both
- Syndromes with ILD involvement
- Diffuse developmental disorder of the lung

Undefined ILD

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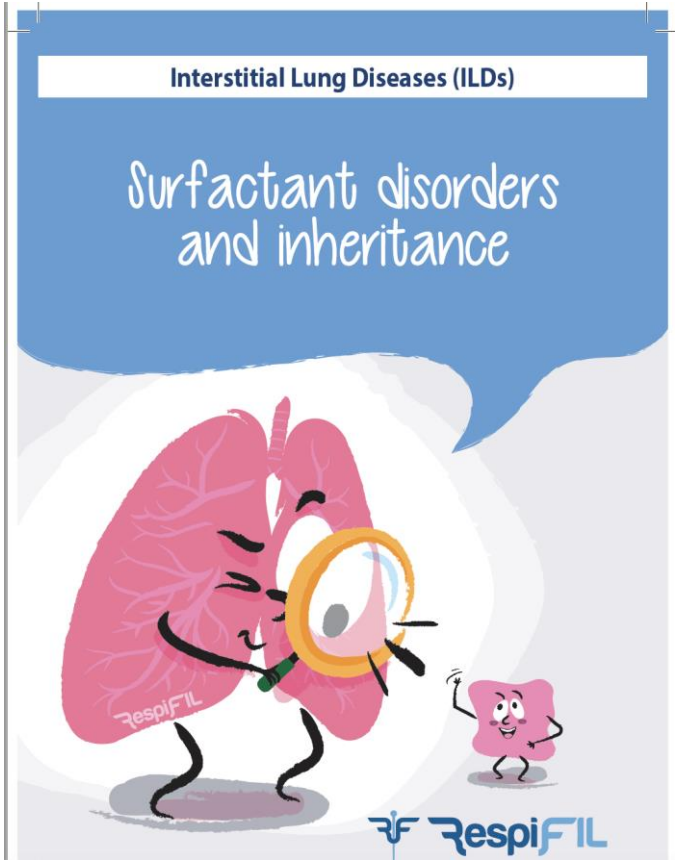


https://respifil.fr/maladies/livrets-information-patients/

ERS

CRC ChILD
European Respiratory Society
Clinical Research Collaboration
Children's Interstitial Lung Disease

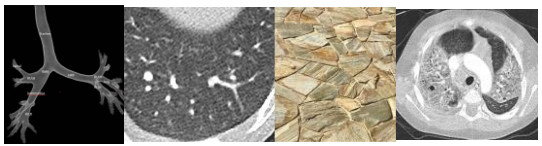
e-learning on thoracic CT-scan in chILD

- Alistair Calder (UK), Chiara Sileo (FR), Nadia Nathan (FR)
- Funded by the French RespiRare network (15,000€)
- Open access, free, with certificate of completion
- Online at the end of 2023

Children's Interstitial Lung Disease
CT Interpretation Guide

Module 1: An introduction to CT techniques in children's lung disease

Children's Interstitial Lung Disease
CT Interpretation Guide



Module 2: Anatomical, pathological and developmental basis for CT signs in ChILD

A case to be discussed? Multidisciplinary team meetings:
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