Pediatric Interstitial Lung Disease

Matthias Griese
Munich

30+10 min
## What is a rare disease? Definition in EU

### Prevalence* of less than 5

<table>
<thead>
<tr>
<th>Examples:</th>
<th>Prevalence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>0.6</td>
<td>1: 3.500</td>
</tr>
<tr>
<td>ABAC3 deficiency</td>
<td>„Rare“/unknown</td>
<td>1: 3.100</td>
</tr>
<tr>
<td>SP-C deficiency</td>
<td>Rare/unknown</td>
<td>1: 1.000.000</td>
</tr>
<tr>
<td>A1AT deficiency</td>
<td>2-5</td>
<td>1: 2.000-5.000</td>
</tr>
<tr>
<td>Asthma COPD</td>
<td>700 (~ 7%) 400 - 1000 (~ 4-10%)</td>
<td></td>
</tr>
</tbody>
</table>

*Calculated from carrier frequencies:
1: 3.100
1: 1.000.000
1: 2.000-5.000

* per 10.000
What is a rare disease?
Definition in Ped Pulm

...diseases of which you,
as a specialized pediatric pneumology center, see
new cases ones or so (none is also possible) per year...

=> The real problems with rare pediatric ILD are
now immediately clear:
Some practical problems - 1

- you have a rare case and need consultation
  ➔ talk to an older specialist in your center or neighborhood who works for 25 years in the field: saw 3 cases

- you can present the very interesting case at the annual meeting of the society, but it is (except for new diseases) almost impossible to publish, although valuable experience/information
  ➔ you pay the 1500 Euro to get the case accepted in BMC case reports
Some practical problems -2

- you want to put together 11x cases with the same diagnosis and see the associated imaging or histology
  ➜ you are lucky as you want to do that only in a single large country;

so you can go to 11x+ radiology and to 11x pathology departments (Attention: some discard material after 10 y)
and try your best.

Fortunately you did consent patients years ago and you have a good chance to recover more than 50% with the help of your data manager who is behind it for a couple of months
Some practical problems -3

• you want to investigate a cohort of 11x patients for common mutations or marker level in lavage or blood
  ➔ you try and find 11x subjects, consent them, get blood from patient and parents (meanwhile divorced)

• you want to explore the unknown natural history of a rare diagnosis using *prospectively* collected data in a relatively large country like Germany
  ➔ impossible
“This is a second opinion. At first, I thought you had something else.”
chILD EU Project

In order to better understand the natural course, risk factors, treatments and reasons for the development of childhood interstitial lung disease (chILD), we will collect and analyse details of symptoms and quality of life, clinical data and also biological material in a Register and Biobank. In the long run this Register will serve the improved understanding of the disease and will lead to the development of new and effective approaches to treatment.

Project Title: Orphans Unite: chILD better together - European Management Platform for Childhood Interstitial Lung Disease

Project No: FP7-305653-chILD-EU

Budget: EURO 3.0 million

Coordinator: Ludwig-Maximilians-University of Munich, Prof. Dr. med. M. Griese

Start: December 2012

Duration: 42 months

Prof. Matthias Griese presented the chILD-EU project during the project’s Kick Off Meeting in Munich which took place on January 18th and 19th 2013 at the Dr. von Hauner Children’s Clinic. Click on image above to view video.

The chILD-EU project is currently comprised of 10 academic partners from 5 European countries.

Our goal is to determine the long term course of childhood interstitial lung diseases (chILD), optimize diagnosis as well as therapy, initiate quality assurance protocols and promote clinical and scientific progress.
**Visit schedule**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Long Term Medication &amp; Effect</th>
<th>BAL / Lung biopsy / Histology</th>
<th>Genetics</th>
<th>Discussion</th>
<th>Diagnoses / Letters</th>
<th>Case Control</th>
</tr>
</thead>
</table>

**Planned visits**

<table>
<thead>
<tr>
<th>Planned visits</th>
<th>Baseline data for peer review and inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.02.2014 - 10:43 (MEZ)</td>
<td>4 weeks 8 weeks 12 weeks 6 months 12 months</td>
</tr>
</tbody>
</table>

**Informed consent / Visit date / Observation type**

- [ ]

**Questionnaires for Patient / Parent reported outcomes**

- [ ]

**Demographics / Initial diagnoses / Family & neonatal history**

- [ ]

**Med. history, Signs, PFT, PHT, Lab., Treatment, Prophylaxis**

- [ ]

**Radiology**

- [ ]

**Peer Review**

- [ ]

**Biomaterials**

- [ ]
Classification of pediatric lung diseases

Airway disorders
- Asthma, obstr.
- Bronchitis, Bronchiolitis
  - Cystic fibrosis
  - Alpha-1 antitrypsin deficiency
  - Primary ciliary dyskinesia

Lung infections
- Pneumonia, Tuberculosis

Pleural diseases

Diffuse parenchymal lung diseases

Localised parenchymal diseases
Diffuse parenchymal lung diseases (DPLD = ILD)

More than 200 entities

A – characteristic for infants

B – all age groups

Griese et al 2009, Orphanet J Rare Dis 4:26
Now 4 y old girl

- Dyspnea with exercise
- Clubbing
- Low breath sounds, some rales
- BAL Pseudomonas/H influenza/PMN´s
- Thrombozytopenia (50,000/μl)
- Normal Karyotype
**A1**
Diffuse developmental disorders

**A2**
Growth abnormalities reflecting **deficient alveolarisation**

**A3**
Infant **chronic tachypnoe** and firm morphology

**A4**
Surfactant dysfunction disorders

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**Postpartal**
Mature, tachypnoea (100/Min), hypoxemia (SaO2 80 %), retractions
⇒ non invasive ventilation d1-d2, O2 until d5, d7 no symptoms, discharged

- Chest x-ray normal

**Some odds:**
- Dentes connati
- Hypertelorism
- Low and dorsally turned ears
- Broad nasal bridge
- Long, flat philtrum
- Small red part of lips
- Prominent frontal head
- Thrombozytopenia (50.000/μl)

Schwerk N et al 2016
A1 Diffuse developmental disorders
A2 Growth abnormalities reflecting deficient alveolarisation
A3 Infant chronic tachypnoe and firm morphology
A4 Surfactant dysfunction disorders

Further history:

- Since month 3 rec. Obstructions/Hypoxämia
- Failure to thrive
- 13 Mon: PDA left->right Shunt, multi-fenestrated ASD, PAH
- 24 Mon: Pneumonia (17d respirator)
A1  Diffuse developmental disorders

A2  Growth abnormalities reflecting deficient alveolarisation

A3  Infant chronic tachypnoe and firm morphology

A4  Surfactant dysfunction disorders

A – characteristic for infants
A – characteristic for infants

A1 Diffuse developmental disorders

A2 Growth abnormalities reflecting deficient alveolarisation

A3 Infant chronic tachypnoe and firm morphology

A4 Surfactant dysfunction disorders

• At age 2 y: 3 generalized seizures

- FLNA p.Tyr2216Leufs*37, het

Filamin A Deficiency
A – characteristic for infants

A1 Diffuse developmental disorders

A2 Growth abnormalities reflecting **deficient alveolarisation**

A3 Infant **chronic tachypnoe** and firm morphology

A4 Surfactant dysfunction disorders

---

Filamin A Deficiency

Lee; Pediatr Radiol (2013) 43:3–13
A1 Diffuse developmental disorders

A2 Growth abnormalities reflecting deficient alveolarisation

A3 Infant chronic tachypnoea and firm morphology

A4 Surfactant dysfunction disorders

Filamin A Deficiency

Filamin A Mutation May Be Associated With Diffuse Lung Disease Mimicking Bronchopulmonary Dysplasia in Premature Newborns

30 wks gest, Birth weight 1730 g
Mild RDS
At 7 months extubated to BIPAP
Pulm. hypertension improved
A – characteristic for infants

**A1**
Diffuse developmental disorders

**A2**
Growth abnormalities reflecting **deficient alveolarisation**

**A3**
Infant **chronic tachypnoe** and firm morphology

**A4**
Surfactant dysfunction disorders

Other associated abnormalities

- **skeletal dysplasia** (MELNICK-NEEDLES)
- Ehlers-Danlos variants and cardiovascular anomalies

➔ Filamin A mutations (FLNA)
<table>
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<th>A2</th>
<th>A3</th>
<th>A4</th>
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**A** – characteristic for infants
Example

- 7 Mon. old boy
- Normal pregnancy/birth
- Month 3: acute upper respiratory tract infection, BF 60/min
- Since then tachypnea
- No fever
- Length 25-50 Perc.,
- Weight 3-10 Perc
- Slight pectus excavatum
Your diagnosis?

- Sub- and inter-costal retractions
- Tachypnea 60-70/Min.
- Crackles
- O2 Sat: 92%
Persistent Tachypnea of Infancy (PTI)

Am J Respir Crit Care Med. 2015
Kids lung register (KLR) 2001 - 2015

All cases of the category: “Specific conditions of undefined etiology“
(=A3, Infant chronic tachypnoe of unknown etiology*)

(n= 89)

Infants with persistent tachypnea and CT scan with mainly ground glass opacities or only minor abnormalities

CT scan available for this study (n=80)

no CT scan available for this study (n=9)
Ground glass opacification

Air-trapping

Usual
Aberrant
Kids lung register (KLR) 2001 - 2015
All cases of the category: “Specific conditions of undefined etiology“
(=A3, Infant chronic tachypnoe of unknown etiology*)
(n= 89)

Infants with persistent tachypnea and CT scan with mainly ground glass opacities or only minor abnormalities

CT scan available for this study (n=80)
no CT scan available for this study (n=9)

Patient has CT scan at diagnosis with **ground glass opacities** confined to middle lobe, lingula, parahilar and paramediastinal areas, no additional abnormalities. (n=50)
Patient has CT scan which may have **ground glass opacities** confined to middle lobe, lingula, parahilar and paramediastinal areas, additional lobes may be involved and other abnormalities may be present. (n=30)

**Usual** persistent tachypnea of infancy (usual PTI)

Lung biopsy
yes (n= 20)
no (n= 30)

n= 14 Neuroendocrine cell hyperplasia of infancy (NEHI)*
n= 7
n= 0 Pulmonary interstitial glycogenosis (PIG)**
n= 4
n= 6 Normal lung tissue***
n= 2

**Aberrant** persistent tachypnea of infancy (aberrant PTI)

yes (n= 13)
no (n= 17)
Rauch et al 2015, Am J Respir Crit Care Med
Rauch et al 2015, Am J Respir Crit Care Med
Summary

-PTI can be diagnosed by
  * typical history
  * clinical findings and a
  * high quality CT scan

-Infants with PTI had the same favorable respiratory and overall outcome
  * if usual or
  * if aberrant (additional local and minor findings)

-The findings were independent on the presence or absence of histology
  ➔ Lung biopsies only in rare complicated cases
| A1  | Diffuse developmental disorders |
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| A4  | Surfactant dysfunction disorders |
A – characteristic for infants

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Pulmonary alveolar proteinosis in children on La Réunion Island
**A** – characteristic for infants

- **A1** Diffuse developmental disorders
- **A2** Growth abnormalities reflecting **deficient alveolarisation**
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**Girl**

- **A** 13 years
- **B**

**9 years**

- **C** 5 years
- **D**

**8 mon**

Enaud et al. Orphanet Journal of Rare Diseases 2014, 9:85
**A** – characteristic for infants

**A1** Diffuse developmental disorders

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Boy 9 mon, Lung post-mortem

Boy 2,9 years, Liver

Micro nodular cirrhosis, steatosis, ductular proliferation without active inflammation

Girl 9 years, OLB

Enaud et al. Orphanet Journal of Rare Diseases 2014, 9:85
Pulmonary alveolar proteinosis in children on La Réunion Island

A – characteristic for infants

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25 years, post-mortem

Enaud et al. Orphanet Journal of Rare Diseases 2014, 9:85
Pulmonary alveolar proteinosis in children on La Réunion Island

Enaud et al. Orphanet Journal of Rare Diseases 2014, 9:85
**Methionyl-tRNA Synthetase (MARS) mutations are the cause of Reunion PAP**

Biallelic variants identified:

<table>
<thead>
<tr>
<th>Region</th>
<th>Variants</th>
</tr>
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<tbody>
<tr>
<td>Homo</td>
<td>c.1031A&gt;G (p.Tyr344Cys)</td>
</tr>
<tr>
<td>Réunion</td>
<td>c.1177G&gt;A (p.Ala393Thr)</td>
</tr>
<tr>
<td>Tunisia</td>
<td>c.1700C&gt;T (p.Ser567Leu)</td>
</tr>
<tr>
<td>France</td>
<td>c.1814A&gt;T (p.Asp605Val)</td>
</tr>
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Structure superimposed with MSA and tRNAMet

_Hadchouel, Wieland, Griese, et al. 2015, Am J Hum Genetics_
<table>
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<tr>
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<th>Related to</th>
<th>Exposition and immune-intact</th>
<th>Immuno-compromised host or transplanted</th>
<th>Related to lung vessels structural processes</th>
<th>Related to reactive lymphoid lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>systemic disease processes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Exposition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Immuno-compromised host or transplanted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Related to lung vessels structural processes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Related to reactive lymphoid lesions</td>
<td></td>
<td></td>
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B  – all age groups
11-year-old boy
- failure to thrive
- dry cough
- exertional dyspnea for 1 year
- second-degree consanguinity
- Malnutrition, clubbing
- O2-sat: 96% => 93% with exertion

CT: fibrotic changes, ggo, 3 nodules
Exclude:
CF, GERD; TBC, bird/fungi exp., viruses, immunodeficiency, heart, ANA etc, histiocytosis (BM)

Lung function:
FEV1 36%, FVC 35%, DLCO: 25% of predicted
6´-walk test: 378 m

Thoracoscopic lung biopsy was performed
Lymphoid follicles around bronchioles and the respiratory bronchioles

Yellow-brown pigmented alveolar macrophages in respiratory bronchioles, alveolar spaces

Minimal chronic inflammation in bronchiolar walls

<table>
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<tr>
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<th>(1) Related to systemic disease processes</th>
<th>(2) Exposition and immune-intact</th>
<th>(3) Immuno-compromised host or transplanted</th>
<th>(4) Related to lung vessels structural processes</th>
<th>(5) Related to reactive lymphoid lesions</th>
</tr>
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</table>

Sismanlar et al; Pediatrics 136, 2015
=> characteristic for RB-ILD

= Respiratory bronchiolitis interstitial lung disease

➡ history revisited: Passive/active smoke exposure?

- 11 people living in the same house
- he was the only child at home
- All adults smoking at home/sharing the same room

Sismanlar et al; Pediatrics 136, 2015
Respiratory Bronchiolitis–Associated Interstitial Lung Disease in Childhood: New Sequela of Smoking

Tugba Sismanlar, MD³, Ayse Tana Aslan, MD³, Haluk Turktas, MD⁵, Leyla Memis, MD⁶, Matthias Griese, MD⁷

First case associated with passive smoke exposure in childhood

Active smoking in adults
1. Lung cancer
2. COPD
3. Smoking-related interstitial lung diseases
   a) desquamative interstitial pneumonia (DIP)
   b) Pulmonary Langerhans cell histiocytosis
   c) Acute eosinophilic pneumonia
   d) RB-ILD
Treatment and course

- Indoor smoking was eliminated precisely
- Methylprednisolone 1 mg/kg/day;
  after 1 mon: all similar (390 m)
  tapered 2\textsuperscript{nd} mon, stopped 7\textsuperscript{th} mon
- 3 years after elimination of smoke exposure, 14-year-old
  no complains
  persistent clubbing
  FEV1: 45%, FVC: 45%, DLCO: 44% of pred.
  6-minute walk test: 770 m
  Chest x-ray / CT similar; no progression
  BMI: 50-75\textsuperscript{th} percentile
  No passive/active smoking (cotinine urine 34 (<500 ng/mL))
Summary

• Rare diseases are only rare when they are not collected
• Classification of pediatric lung diseases - Examples
  • Filamin A deficiency
  • Persistent tachypnea of infancy
  • Pulmonary alveolar proteinosis due to MARS mutations
  • Respiratory bronchiolitis-associated interstitial lung disease
• European management platform – participate, can have a national coordinator, build up reviewer teams, …
**Acknowledgements**

**Members of the Clinical Study-Groups of the kids-lung-register and the chILD-EU project**

Lab/Register/Biobank
Traudl Wesselak
Andrea Schams