Congenital lung anomalies (CLA) with prenatal diagnosis multicentric database

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Congenital lung anomalies (CLA)

• Malformations arising from lung parenchyma:
  – CPAM (congenital pulmonary airways malformation)
  – Sequestration
  – Pulmonary emphysema (lobar or segmental)

• Malformations arising from bronchial tree:
  – Bronchogenic cyst
  – Bronchial atresia (+/- distal)

_Frequent combination??_
CLA: knowledge and limits

Unfrequent pathology (1.05-1.32/10’000 live birth Eurocat network 2010-2012)

Physiopathology not clearly explained
  • Different growth factors targeted (FGF10, KGF, PDGF)

Natural evolution not clearly known
  • Complications rates, tumoral degeneration?
  • Accuracy of radiological images to predict evolution
Goal of the CLA multicentric database

• Clinical and epidemiological questions:
  ✧ To evaluate prevalence in Switzerland;
  ✧ To analyze the evolution with or without surgery;
  ✧ To correlate radiological with clinical data;
  ✧ To establish long term follow-up for individuals at risk of complications;
  ✧ To evaluate patients having benefit from prophylactic surgery.

• Research questions:
  ✧ To precise histology and subtype incidence;
  ✧ To identify abnormal genomic and proteomic profile of the lesions;
  ✧ Growth factors implications in CLA.
Multicentric ?
Number of case/year?

- 1-4/year
- 2-4/year
- 2-5/year
- 4-5/year
- 2-5/year
CLA follow-up

- Multicentric anonymous database to register prospectively
  1) Clinical
  2) Radiological
  3) Biological and histological data
- From prenatal period to age of 15 years
Multicentric CLA study: prospective cohort study

**Technical aspect:** Developed under SecuTrial®
Providing secure and remote access

**Implementation:** first deployment at Geneva’s in April 2015

**Data population:** pediatric patients with CLA identified since 2012, *with* or *without* surgery performed
Geneva’s pluridisciplinary team

- **Surgeons:** Dr I. Vidal
  Prof B. Wildhaber

- **Pulmonologists:** Dr I. Ruchonnet-Métrailler
  Prof C. Barazzone Argiroffo

- **Obstetrician:** Dr G. Pellegrinelli

- **Pathologist:** Dr AL. Rougemont

- **Radiologist:** Dr M. Anooshiravani-Dumont

- **Technical help:**
  Secu Trial and Clinical Data Manager: K. Mostaguir
  Database implementation and laboratory analysis: J. Lascano Maillard
Usual management at Geneva’s

- Prenatal consultation(s): by surgeon and pneumologist
- Visit of the baby at birth +/- Chest X-Ray
  - If asymptomatic
- First consultation at 1 month +/- Chest X-Ray
  - If symptomatic: earlier CT-scan/surgery
- Thoracic CT-scan around 6 months
- If surgery: around one year-old

Discussion of the study and consent
1) CLA database: Clinical Data

Prenatal

- 18-22 WG Data + US
- 24-28 WG Data + US
- 29-32 WG Data + US
- 33-37 WG Data + US

+ Parental consent
+ Family history/pregnancy

Birth
No surgery

12 months

Surgery

Post-surgery

24 months

Data

Long term data

Pulmonary function

Post-op 1 month data

Post-op 6 months data

Post-op 12 months data

+/- Chest X-Ray + Histology

Chest X-Ray

Chest X-Ray

+= consultation

10 yr
15 yr
6 yr
2) CLA database: Radiological Datas

• Radiological images (Prenatal ultrasound, Chest X-Ray and Thoracic CT-Scan) are stored in a secure server in Geneva;

• Patient’s images are anonymized before storage in a DICOM format;

• Access to the server by each radiological team participating to the CLA database.
3) Biobank logical and Histological datas

Histological data

- Slides reviewed and re-classified by the pathologists (each center in collaboration with the different referent pathologists).

Biobank:

- Lung tissue frozen;
- FFPE slices;
- Blood and frozen tissue if available.
3) Biobank logical and Histological datas

CLA phenotypes analysis based on

- Malformative lung tissue and blood samples collection (approved by local ethical committee);
- Classification of the different malformation under only histological description.

3 different levels of analysis possible:

Genomic-transcriptomic-proteomic
• **Genomic:**

Absence of DNA anomalies in the literature except for trisomy 13, 18 and 21

Localized lesions

  - Turanet *et al.* *Turkish J. of Ped* 2011
  - Heling *et al.* *Prenatal Diagnosis* 2002

• **Transcriptomic**

Some studies with RT PCR performed targeting transcription factors

  - Jancelwicz *et al.* *Pediatric surgery* 2008
  - Lietchy *et al.* *Pediatric Surgery* 1999
• **Proteomic analysis:**
  • Protein extraction of the lesion and the health adjacent tissue (Mass spectrometry)

**Target:**
- Growth factors (FGF-10, FGF-7, PDGF-BB, VEGF, Sox.2, Hoxb5, PCNA)
- Apoptotic and proliferative pathways
- Cell cycle markers
- Lung stem cells

Confirmation of results by Immunohistochemistry and spectrometry on slides.
CLA Database: Facts and Agenda

Spring 2016:
- Lausanne Ethical committee (simplified process)
- Deployment at the CHUV

Winter 2016:
- Possible deployment in different Swiss University Hospitals
- Ethical committee (simplified process)
What is needed from each center for a simplified submission?

- Define referents:
  - Main investigator (Good Clinical practice and CV);
  - Co-investigators:
    - Pneumologist/ surgeon
    - Radiologist
    - Obstetrician
    - Pathologist
    - Neonatologist (optional)
  - One or two referents for parents’ information letter;
What is needed from each center for a simplified submission?

- Parents’ information and consent letter, with local headed paper and signatures;

- We will transmit these names and documents to Geneva’s local committee, and Geneva’s local committee will submit the protocol to your local committee.
Thanks

At Geneva:
Dr I. Vidal
Prof B. Wildhaber
Prof C. Barazzone Argiroffo
Dr G. Pellegrinelli
Dr AL. Rougemont
Dr M. Anooshiravani- Dumont

K. Mostaguir
Dr J. Lascano Maillard

All teams met at Lausanne, St-Gallen, Basel and Bern.
Questions ?
CLA : Blood and Tissue Biopsy

Old cases:

1) Paraffin tissue section analysis
2) Blood sample 5ml/EDTA for DNA analysis

New cases:

1) Frozen a section with OCT in cryomold and stored at -80° for *immunohistochemistry* and *DNA*;

2) Frozen a section at -80° for *DNA* and *protein*;

3) Blood sample 5ml/EDTA for *DNA* analysis.
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