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Observational Study of Familial Concordance in Primary Ciliary Dyskinesia (PCD)

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Other investigators who already expressed interest in the study:

N/A

Other Possible participating partners:

- All ERN-LUNG (European reference network) members and affiliated or supporting partners

- All members of BEAT-PCD and BESTCILIA

Authorship suggestion:

Data providers and departments involved in the study will be offered a co-authorship according to the **criteria of the International Committee of Medical Journal Editors**, which include all the following:

i) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;
ii) drafting the work or revising it critically for important intellectual content;
iii) final approval of the version to be published; and
iv) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Participating centres are offered a maximum of three co-authorships (1: > 5 PCD patients; 2: > 15 PCD patients; 3: > 30 PCD patients, 4: > 100 patients) among investigators. All other partners and collaborators contributing to this trial shall be duly acknowledged in the publication.

Background

Primary Ciliary Dyskinesia (PCD) is a rare hereditary disease caused by mutations in more than hitherto known 40 causative genes, which is characterized by wide phenotypic variability in its diagnostic and clinical manifestations [1]. A few studies have addressed the correlation between pathogenic variants in certain PCD genes and clinical manifestations [2,3,4]. Clinical and phenotypic variability has also been observed within small cases series bearing the same genotypic defect [4, 5,6,7]. The extent of phenotypic variability in patients with identical genotypic variant is currently unknown. Other factors such as modifier genes, environmental conditions, acute and chronic infections and access to healthcare, may well influence clinical disease severity in PCD patients. A study in PCD siblings of the diagnostic and clinical phenotype will enable the assessment of the disease phenotypic variability in the presence of the same genetic defect and environmental conditions, at least in childhood.

Aims

The aims of this paper are:

1. To assess agreement within sibling-pairs (and by affected sibling birth order and by affected sibling age of diagnosis where applicable) of phenotypic characteristics such as:
    a. diagnostic results (nasal NO, TEM, ciliary beat frequency and pattern)

b. age and symptoms at presentation including *situs*, CHD

c. Neonatal symptoms and course of clinical manifestations (e.g. course of infections, presence of bronchiectasis)

2. To assess the correlation within sibling-pairs in terms of lung function measurements (FVC and FEV1), both cross-sectionally and longitudinally (if possible, by when siblings live together and after living apart)

3. To assess whether correlation within sibling pairs in terms of lung function measurements (FVC and FEV1) differs by gender concordance

4. To assess *Pseudomonas aeruginosa* cross infections in families (if possible, by when siblings live together and after living apart)

Methods

Study design and study population:

Retrospective observational multi-centre cohort study.

Basic Inclusion Criteria:

i) Patients are siblings originating from the same biological parents.
ii) Patients with a genetically confirmed diagnosis of PCD (bi-allelic mutations in a gene, known to cause PCD) with typical clinical symptoms of PCD,
Or
iii) Patients with typical clinical symptoms of PCD and at least two other methods (TEM, HSVM, NO and IF) confirming PCD-diagnosis but without genetic diagnosis.

Desirable Additional Data:

iv) Cross-sectional spirometry measurements available for more than one sibling.
v) Longitudinal datasets with measurements of lung function (FEV1, FVC, with date and height at the performed measurement, respectively)
vi) At least 3-4 different spirometry measurements in at least 2 years of follow up are expected – in cases where this is not possible, sporadic data could also be provided

Data Collection:

We will use the dataset already generated for the purposes of the "International study on genotype/phenotype correlation with focus on lung function in patients with Primary Ciliary Dyskinesia (PCD)". Participating centers will have to indicate pairs (triplets or more) of siblings already part of the dataset. The study coordinators may request additional data such as the course of infections, status of *Pseudomonas aeruginosa* and/or presence of bronchiectasis, time of stop living together, *via* a dedicated excel template, if required. For patients that do not have genetic

diagnosis and/or spirometric data, all necessary data will be requested through direct contact with participating centers.

Statistical Analysis

The agreement of categorical (binary) phenotypic characteristics within the sibling pairs will be assessed using the Cohen's Kappa statistic while the weighted Cohen's Kappa statistic will be used for the assessment of agreement for categorical (ordinal) characteristics. The agreement of continuous variables within the sibling pairs will be assessed using the Intraclass Correlation Coefficient. Lung function variables will be converted into sex-, height-, age- and ethnicity adjusted z scores using the Global Lung Initiative [8]. For the longitudinal analysis, FEV1 z-score and FVC z-scores trajectories versus age will be expressed as slopes. The agreement of slopes within the sibling pairs will also be assessed using the weighted Cohen's Kappa. The analysis will be repeated for sibling pairs that are gender concordant and gender discordant.

Ethical Considerations

Each study partner will have to ensure they have the appropriate Ethics and Research & Development approvals from their institution and national governing bodies.

Data safety and data handling

The dataset that will be used for this study will be anonymized and standardized according to ERN-LUNG data safety measures

Target Journal(s):

European Respiratory Journal, Thorax, Chest, Respiratory Research in the mentioned order of priority.

Milestones:

- 30 September 2020: Finalization of the participating centers
- 31 December 2020: Data cleaning and finalization of study dataset
- 31 March 2021: End of data analysis
- 31 May 2021: Circulation of first draft

References

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