Sylvana M. Hidalgo, MD
Originating Department: Pediatric Cardiology
Submitting to: Medical Center
Title: Single-Center Description of Clinical Presentation of Pulmonary Hypertension in Patients Also Diagnosed with Connective Tissue Disease.
IRB: Columbia University Medical Center

STUDY DESCRIPTION

Background information, study purpose and study rationale

Pulmonary hypertension is a disease that was first documented in 1891 in a publication that described "arterial thickening" post-mortem,[1] but it was not until 1951 that the term "primary pulmonary hypertension" was used in the literature[2, 3] and pulmonary hypertension as a disease entity began to take shape. Despite early attempts, it remained poorly understood until recent efforts in the past decade were made to better characterize the patient population and to lay the groundwork for further study.[4,5]

Both adults and children are diagnosed with pulmonary hypertension according to the following criteria: mean pulmonary artery pressure ≥25 mm Hg at rest (> 30 during exercise), pulmonary capillary wedge pressure ≤15 mm Hg, and increased pulmonary vascular resistance (in pediatrics, >3 Wood units is used).[6] The disease course itself can vary significantly based on the clinical classification first made in 1973, which was further delineated during a pulmonary hypertension world symposium in 2008.[7] Classifying pulmonary hypertension into discrete groups has paved the way for more in-depth research of the pathophysiology and subsequent treatments, leading to improved patient outcomes for some groups of pulmonary hypertension.[8] Unfortunately for the pediatric population, most of the research in the field has been focused on the adult population, and although some of the data can be extrapolated to caring for pediatric patients, very little has been validated.[6]

The two registries that have provided the most insight into the disease in pediatrics are the REVEAL (Registry to EValuate Early And Long-term pulmonary arterial hypertension disease management) registry[9] and the TOPP (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension) registry.[10] REVEAL sought to characterize both adult and pediatric patients in the World Health Organization (WHO) group 1 PAH, while TOPP described all pediatric patients diagnosed with pulmonary hypertension regardless of group designation. Connective tissue disease (CTD), which falls under the group 1 PAH designation, has been long implicated in pulmonary hypertension pathophysiology, yet the percentage of adult pulmonary hypertension attributed to CTD has varied from ~8-30%.[4, 11-12] The percentage in pediatrics has been less studied, with TOPP identifying 3% of pulmonary hypertension attributed to CTD.[10] Significant effects on morbidity and mortality have been demonstrated in adult patients with CTD who develop pulmonary hypertension. Two-year survival rates for such patients have been estimated to be between 40% and 50%, compared with survival rates of 80% for CTD patients without pulmonary hypertension.[13,14]

Despite this significant association in adults, little has been studied in pediatric patients with pulmonary hypertension attributed to CTD. Our pediatric pulmonary hypertension center at NYP-Columbia Children's Hospital of New York sees a large cohort of such patients, and anecdotal evidence suggests an association between pulmonary hypertension and CTD that may be greater than the 3% association identified in the TOPP study. Our study seeks to present a single-center description of the clinical presentation of pulmonary hypertension in patients with connective tissue disease, to describe management principles of our department, and to discuss outcomes broadly. We anticipate approximately 25 patients in our database. We hope to provide the field with more information on the appropriate management of this cohort of patients to improve outcomes and guide clinical practice.

Although there has been much work done to compile registries of pediatric pulmonary hypertension patients to gather better demographics and characteristics of patients worldwide, there is a paucity of research on specific patient presentations and the field lacks a set of clinical guidelines that should be adopted in every patient presenting with pulmonary hypertension.[15] Ultimately, this knowledge could contribute to the assessment of prognostic factors and lead to treatment advancements in the future.

STUDY DESIGN/STATISTICAL PROCEDURE

We aim to describe the pediatric patients with pulmonary hypertension also found to have connective tissue disease diagnosed between January 1, 2005 and January 1, 2015. Age range will include 3 months to 24 years, males and females with a confirmed diagnosis of pulmonary hypertension and connective tissue disease. The order in which each disease was diagnosed will not effect participation in the review. Connective tissue disorders studied will include systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease, dermatomyositis, rheumatoid arthritis, and macrophage activation syndrome. We anticipate approximately 25 patients in our database, combining patients treated in both pediatric pulmonary hypertension center and Adult Rheumatology Division of NYP-Columbia. An in-depth chart review will be performed to assess clinical presentation of pulmonary hypertension, what studies were done to confirm diagnosis, CTD status of the patient at that time and subsequently, management/treatment received and outcomes.

Statistical procedure: analyze data in several ways

1. Of all the patients with pulmonary hypertension in our registry, is there a difference in levels of ANA that can predict severity of CTD or development of CTD in the future?
    a. We would test this hypothesis utilizing a T test to analyze if there is a difference between ANA mean in patients with CTD and ANA mean in patients without CTD.
2. Of the pediatric patients with pulmonary hypertension, what percentage also has CTD?

a. We would calculate the number of patients with PH and CTD and compare to total number of PH patients then construct a confidence interval to compare to adult percentage.
b. We could also construct a chi-squared test to assess the difference between adults and pediatrics

STUDY LOCATIONS

NYP- Columbia Medical Center, Pediatric Pulmonary Hypertension Center and Adult Rheumatology Division.

STUDY SUBJECTS: INCLUSION AND EXCLUSION CRITERIA

1. Inclusion
    - Patients between 3mos and 24 years of age
    - Patients diagnosed with both pulmonary hypertension and connective tissue disease (SS, SLE, MCTD, DM, RA, MAS), regardless of which occurred first between 1/1/05 and 1/1/15.
2. Exclusion
    - incomplete diagnosis
    - missing diagnostic data

STUDY PROCEDURES

Retrospective chart review of all pediatric patients with pulmonary hypertension and connective tissue disease age 0-24 years during the period 01/01/2005 – 01/01/2015 at NYP-Columbia Medical Center.

Data to be obtained:

1. Age at presentation
2. Comorbidities
3. Presenting symptoms
4. Medications at time of presentation
5. Work up at time of presentation: CXR, EKG, Echo, ANA, BNP, Right heart catheterization
6. Identify treatments administered to treat pulmonary hypertension.
7. Clinical status at 1/1/15

RECRUITMENT

Patients will be recruited from a database of pulmonary hypertension patients maintained by the Pediatric Pulmonary Hypertension Center as well as from the Adult Rheumatology division of from Columbia Medical Center over a 10-year period, from January 2005 to January 2015 and whose ages are between 3 months to 24 years. Patients who meet inclusion criteria will be contacted and asked to give permission to perform an in depth chart review.

CONFIDENTIALITY OF STUDY DATA

We will formulate a coding system for patients, which is independent of identifying information. All recorded and compiled confidential medical information will be de-identified via removal of subject name, hospital unit number, telephone number(s), and address(es), thus constructing a completely de-identified database. Identifiers will be listed on a document that matches each patient with a unique identifier. This document will be encrypted and will remain separate from the database on a secure, encrypted computer in the Division of Pediatric Cardiology. Any identifiers will be destroyed at the conclusion of research.

POTENTIAL RISKS

None, as this is a retrospective observational study.

POTENTIAL BENEFITS

None to study subjects, though potentially beneficial to future patients.

ALTERNATIVES

Not describing our patient population with PH and CTD.

COMPENSATION TO SUBJECTS

None, as this study is retrospective.

COSTS TO SUBJECTS

None, as this study is retrospective.

MINORS AS RESEARCH SUBJECTS

This study is a retrospective observational study involving data obtained from the medical records of minors. Approval from the Department of Pediatrics Committee on Human Investigation will be obtained prior to the initiation of the study.

RADIATION OR RADIACTIVE SUBSTANCES

No radiation or radioactive substances will be used in this study.

CONSENT ISSUES

Minimal risk to subjects, parental consent will be sought in patients 17 years of age or less. Consent will be obtained from patients 18 years or older.

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