

Thyroid Disease and Pulmonary Hypertension.

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A. Study Purpose and Rationale:

Pulmonary arterial hypertension (PAH) is a disease of the pulmonary vasculatures characterized by elevated pulmonary arterial pressures leading to right heart failure. There are five major categories of pulmonary hypertension. The first category known as PAH includes diseases in which the primary abnormality is in the small pulmonary arteries. Groups 2 through 5 of Pulmonary hypertension include pulmonary hypertension with left heart disease, pulmonary hypertension with lung disease and or hypoxemia, pulmonary hypertension due to chronic thrombotic and or embolic disease or miscellaneous. For this study we are concentrating on the first group of patients. In this group vascular injury to the small pulmonary arteries can be either idiopathic or it can be secondary to other diseases or other exposures. Pulmonary hypertension caused by known causes is called secondary hypertension. Examples of such secondary causes include examples include those associated with collagen vascular disease, congenital systemic to pulmonic shunts, HIV infection, drugs and toxins (such as amphetamines and anorexigens). These known exposures do not always cause pulmonary hypertension, but instead are associated with the disease and are thought to be related to the pathophysiology of the disease. Those cases of hypertension without known causes are called primary or idiopathic. There are also familial forms of PAH. Mutations in the gene for bone morphogenetic protein receptor type 2 have been associated as the main cause of inherited PAH. It is inherited as an autosomal dominant trait with about 20% penetrance. Some patients with sporadic PAH also are found to have BMPR2 mutations. ⁱ

The pathophysiology of PAH is not known. It is believed that genetic factors involved in immune dysfunction may be related. Many of the features of autoimmune disease are found in PAH patients: There are more females than male patients, there are HLA types that are linked to the disease, PAH is often found in connective tissue disease, the disease is treated with immunosuppressive treatment, and auto antibodies are often found in the serum of these patients. These findings along with the BMPR2 findings suggest a genetic component to PAH; however there must also be environmental factors. The incomplete penetrance of BMPR2 suggests that the mutation is necessary but not sufficient for disease. Other factors are necessary for disease presentation. ⁱⁱ

Prior studies have demonstrated an association between thyroid dysfunction and PAH. Earlier studies showed a relationship between hyperthyroidism or hypothyroidism. These studies were retrospective and showed a correlation of PAH to either elevated or diminished TSH levels. ^{iii iv} Another retrospective study showed a high level of thyroglobulin autoantibodies in patients with PAH. A study in 2002 tried to combine the different categories of thyroid disease. They took Graves hyperthyroidism, Hashimoto hypothyroidism, and thyroid Autoantibodies to represent overlapping conditions in the autoimmune thyroid disease (AITD) syndrome. They did a prospective study of people with PAH who were followed with TSH and T3, T4 tests as well as tests for thyroid antibodies. They showed a 49% prevalence of AITD in PAH patients (69% AITD in

idiopathic PAH patients). The results were stratified as to secondary causes of pulmonary hypertension and primary pulmonary hypertension.^v The study's findings were compared to the Colorado cohort's findings of thyroid dysfunction without age, race, or sex matching.^{vi}

The goal of this study is to discover the prevalence of thyroid disease in PAH patients as compared to a control population. Thus, it will be a case-control study. We hypothesize that there will be a higher prevalence in the PAH patients than in the control population. Such a finding would further elucidate the pathophysiology of PAH, although further studies would be needed to determine the significance of the relationship between these diseases. This would confirm the findings of the 2002 group while providing a better control population. A secondary goal would be to look at subjects with BMPR2 mutations with and without pulmonary hypertension to see if the prevalence of thyroid disease was different between the two groups. Due to the fact that the prevalence of thyroid disease is much greater in idiopathic PAH and that BMPR2 mutations have been found in 10-25% of cases of sporadic PAH and in 60% of familial cases, it is possible that thyroid function may be a factor that leads to increased penetrance of thyroid disease.

B. Methods.

Study Design.

This study will be a case controlled study. The cases will be taken from patients enrolled in the genetics of pulmonary hypertension study. These patients will be identified by right sided cardiac catheterization. Patients with primary pulmonary hypertension (as determined by the absence of other secondary factors excluding thyroid disease) will be included in the study. These patients will be given or sent a questionnaire asking about their disease and any co morbid conditions that they have been diagnosed with. Included in this questionnaire is a question about hyperthyroid and hypothyroid disease. Also included are questions asking about other secondary causes of pulmonary hypertension. Patients are asked to fill out this questionnaire and return it to the program. Over 100 questionnaires were given to patients at the pulmonary hypertension convention. Other questionnaires have been sent out to participants already enrolled in the study. Using the questionnaire data, the prevalence of thyroid disease in the patients with primary pulmonary hypertension will be calculated.

The controls will be chosen from people with asthma diagnosed with pulmonary function tests. This is to avoid incorrect diagnoses of asthma. These controls will be age, sex, race, and socioeconomic class matched to the cases. There will be 1 control for every case. These patients will have blood tests to check for TSH, T3, T4 and antithyroid antibodies. Patients with blood tests significant for hyper/hypothyroid disease will be labeled as AITD, and the prevalence of AITD in this population will be determined.

A nested study would be to look at BMPR2 positive patients with both clinical PAH and no PAH. Using the same data questionnaires, the prevalence of thyroid disease can also be ascertained in these 2 groups. Patients familial pulmonary hypertension have already been enrolled in the PAH genetics study along with their family members. During the enrollment process, they sent in samples of blood to be tested for the BMPR2 mutation. DNA is extracted from the blood, the BMPR2 gene is amplified and then

sequenced for a mutation. These patients and their families have been sent questionnaires to determine if they have ever been diagnosed with thyroid disease.

Power analysis

A chi square analysis was be used to calculate the number of participants. 42 in each group are needed to detect a 25% difference between the 2 groups for the primary outcome. The 25% diffence was estimated based on the 2002 study.

For the secondary outcome, it has been previously published that first degree relatives of patients with PAH have of prevalence of thyroid disease of 25%. If we assume that the BMPR2 carriers have this prevalence and the BMPR2 patients with PAH have the prevalence of patients with IPAH found in the 2002 study of 67%, 25 people are needed in each subgroup to get a statistically significant result.

C. Study procedure.

Questionnaires and DNA collection kits (either blood or saliva) are given to cases, controls and members of BMPR2 positive families with no disease.

D. Study Drugs.

There are no study drugs involved in this study design.

E. Medical device.

There are no medical devices involved in this study design.

F. Study Questionnaires

Please see attached sample questionnaires.

G. Study Subjects.

Study subjects will be as discussed above. The study subjects are people with Pulmonary Hypertension diagnosed by right heart catheterization. The control group are people with asthma diagnosed by pulmonary function tests who are age and sex matched to the case group.

For the secondary outcome, the study subjects are BMP-R2 positive patients with PAH diagnosed by right heart catheterization. The control groups are patients with BMP-R2 mutations who do not have pulmonary hypertension.

H. Recruitment of Subjects

Potential subjects will be approached through clinical visits and at PAH meeting

I. Confidentiality of Study Data.

Subject will given a study number, linking the swab/consent/ and questionnaire information. Data will be stored at a secure location.

J. Potential Conflict of Interest.

The investigators have no known bias to report at the time of this study.

K. Location of the Study.

The location will be at Columbia University Medical Center.

L. Potential Risks.

There are little risks to the subject population during this prevalence study.

M. Potential Benefits

The potential benefits are those of further understanding the pathophysiology of PAH. No direct

N. Alternative Therapies

No alternative therapies apply.

O. Compensation to Subjects

Compensation to subjects will involve \$5 for control population

P. Costs to Subjects

There are no costs to the subjects.

Q. Minors as Research Subjects

Minors with PAH will be part of this study. Efforts to get blood samples during catheterization will be used. Saliva kits will also be used to obtain DNA when possible.

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R. Radiation or radioactive Substances

Not used in this study

References

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