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Decreased Mortality of Pulmonary Arterial Hypertension in Duchenne Muscular Dystrophy and Down Syndrome

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Abstract

The genetic cause of significant disorders like Down syndrome (DS) and Duchenne muscular dystrophy (DMD) is well documented. Pulmonary arterial hypertension (PAH), a co-morbid condition, is tied to mortality among these groups. Individuals with the ability to communicate their symptoms and actively participate in treatment are at an advantage with subsequent benefit. DS and DMD significantly decrease physical ability and communication capacity. Genetic research has allowed for earlier identification of, or predisposition for, the development of PAH. Work has also progressed toward manipulation at the genetic level to decrease the severity and even eradicate the cardiopulmonary disorder. This information is beginning to be applied in treatment for individuals with PAH. A literature review was conducted to identify the research, prediction methods and treatment of PAH in individuals with Duchenne muscular dystrophy (DMD) and Down syndrome (DS) as it relates to decreased mortality or increased life expectancy among those groups. The results showed significant gains in the understanding of PAH, DS and DMD individually. There was little evidence of research focusing on PAH as it pertains particularly to DS or DMD.

Introduction

The 5th World Symposium on Pulmonary Hypertension, held in Nice, France, February 27 to March 1, 2013, identifies four specific types of PAH: Idiopathic, Familial, Drug or Toxin Induced and Associated. Idiopathic PAH (IPAH) causes are unknown (Saji, 2014). Familial PAH (FPAH) has a genetic cause (Chew, Loyd & Austin, 2017). Drug or Toxin Induced PAH is a growing concern (Peacock, Murphy, McMurray, Baballero & Stewart, 2007). The most common type of PAH, associated (APAH), occurs along with other medical conditions (Chew et al., 2017)

Recent studies have provided insight in the diagnosis and screening for both familial and associated pulmonary arterial hypertension. Research has led to earlier diagnosis of and screening for PAH (Tonelli et al., 2013).

Unfortunately, co-morbid and/or exacerbating conditions often dictate patient outcome (Tonelli et al., 2013). Many disorders of the body cause APAH. Two genetic conditions having co-morbid occurrence of APAH are Down syndrome and Duchenne muscular dystrophy. Both of these disorders have high mortality rates.

Statement of the Problem

Identifying the specific underlying pathophysiology and etiology of PAH when associated with DMD and DS is vitally important to treatment. It is also important to understand that options with proven, evidence-based modalities particular to co-morbid conditions can have positive influence on patient outcomes, from increased life expectancy to improved quality of life. Reviewing research which has been completed helps deepen the understanding of the direction future investigation in PAH is taking.

Research Questions

- What is the correlation between genetic disorders like DMD and DS with increased incidence of PAH?
- What has current and existing research shown in the understanding of pulmonary arterial hypertension?
- What is the recommended, evidence based treatment modality for PAH specific to DMD and DS?
- Among individuals with Duchenne muscular dystrophy and Down syndrome with co-morbid pulmonary arterial hypertension (PAH), has early recognition and treatment led to statistically significant increase in life expectancy versus previously undiagnosed or unrecognized PAH?

Literature Review

Correlation between DMD or DS and incidence of PAH
DMD progresses with muscle wasting and connective tissue disorders. These processes result in eventual dystrophy of the diaphragm and pneumonia. A study comparing thirty-one individuals with DMD and eleven healthy individuals has shown a significant correlation ($r = -0.384$, $p = 0.0391$) between plasma nitric oxide levels and ejection fraction measured by echocardiogram in the DMD group (Kasai et al., 2004). The finding suggests that there is a significant decrease in production of nitric oxide as part of the disease process of DMD. Decreased levels of nitric oxide have a direct effect on prostacyclin and a converse effect on endothelin. A study of eight individuals with advanced development of DMD were evaluated by right heart catheterization. A mPAP of > 20 mmHg was noted in all subjects, while five of the eight had a mean pulmonary arterial pressure of > 40 mmHg (Yotsukura, Miyagawa, Tsuya, Ishihara & Ishikawa, 1988).
The majority of CHD in Down syndrome are related to septal wall and atrioventricular valve defects (Li et al., 2012). From May of 2007 to December of 2008, 704 patients with congenital heart defects were studied to identify independent risk factors of PAH in CHD. Logistic regression analysis revealed that age, systemic artery systolic blood pressure, VSD, PDA and combined lesions were independent risk factors of PAH in CHD (Li et al., 2014).

Literature Review Continued

Current Understanding of PAH

- The Pulmonary Hypertension Association summarized the pathophysiologic pathways of PAH at its 2017 symposium:
  - **Nitric oxide (NO)**: An endogenous pulmonary vasodilator; also possesses anti-proliferative properties. A relative deficiency of endothelial NO in the pulmonary vasculature may be one mechanism which contributes to the development of PAH.
  - **Endogenous prostacyclins**: Systemic and pulmonary vasodilators, anti-proliferative agents that also have antithrombotic/antiplatelet effects. Relative deficiency or down-regulation of endogenous prostacyclin may contribute to the development of PAH.
  - **Endothelin-1**: An endogenous vasoconstrictor. Up-regulation of endogenous endothelin-1 may also contribute to the pathogenesis of PAH.
- The small vessel arteriopathy in PAH leads to a progressive rise in RV afterload and pulmonary vascular resistance (PVR). As a result, the RV undergoes remodeling changes, including right ventricular hypertrophy, dilatation and finally dysfunction. If PAH is left untreated, right ventricular failure will ultimately result in patients experiencing syncope, angina, edema and abdominal distention (Favilli et al., 2015). Right ventricular failure is the most common cause of death in patients with PAH (Sitbon and Morrell, 2012).
- BMPR2 epistatic effect on KCNK3 and TGF-Beta resulting in smooth muscle potassium and calcium channelopathy (Ma et al., 2013).
- PDLIM5 protein is produced in the smooth muscle cells of the pulmonary artery (Zhou, Chen and Raj, 2015). Within the past year the American Lung Association has begun investigating the effect hypoxia has on the PDLIM5 expression. Of particular note is the suppressive effect PDLIM5 plays on the activation of a downstream protein SMAD2/3, which is responsible for cell signaling in smooth muscle (Ousterout et al., 2015). This study is scheduled to conclude in 2019.

Discussion

Although there has been significant research in regard to DMD, DS and PAH individually, limited study has occurred on the correlation between either of the special populations and PAH. Furthermore, it would seem that there are no reported studies on the life expectancy or quality of life related to early intervention and treatment pertaining to individuals with DMD or with DS. The commonality of the pathophysiologic processes involved in PAH, regardless of co-morbid conditions, is the profound take away. Evidence-based treatment algorithms are available for PAH, centered around the functional classification of the patient.

Applicability to Clinical Practice

- Supportive therapy and general measures with expert referral upon suspicion.
- Advanced therapies initiated with confirmation through right heart catheterization and vasoreactivity testing.
- Treatment is centered around the individual's limitation of physical activity.
  - Individuals that demonstrated a vasoreactive response are treated with calcium channel blockers.
  - Individuals that do not demonstrate a vasoreactive response:
    - PH with slight limitation- Ambrisentan & tadalafil
    - PH with marked limitation- Ambrisentan & tadalafil
    - No improvement or deterioration- double or triple therapy
- Key to treating individuals with DMD or DS is the recognition of changes in behavior and activity by the provider

References

Chew, Joshua D., Loyd, James E., and Austin, Eric D. (2017). Genetics of Pulmonary Arterial Hypertension. *Seminars in Respiratory Critical Care Medicine 38(05)*,585-595. doi:10.1055/s-0037-1606201

Favilli, S., Spaziani, G., Ballo, P., Fibbi, V., Santoro, G., Chiappa, E., and Arcangeli, C. (2015). Advanced Therapies in Patients with Congenital Heart Disease-Related Pulmonary Arterial Hypertension: Results from a Long-Term, Single Center, Real-World Follow-Up. *Internal Emergency Medicine. 10*, 445–450. doi:10.1007/s11739-014-1185-1

Kasai, T., Abeyama, K., Hashiguchi, T., Fukunaga, H., Osame, M., and Maruyama, I. (2004). Decreased Total Nitric Oxide Production in Patients with Duchenne Muscular Dystrophy. *Journal of Biomedical Science. 11*, 534–537. doi:10.1159/000077905

Li, H., Cherry, S., Klinedinst, D., DeLeon, V., Redig, J., Reshey, B., Chin, M.T., Sherman, S.L., Maslen, C.L., and Reeves, R.H. (2012). Genetic Modifiers Predisposing to Congenital Heart Disease in the Sensitized Down Syndrome Population. *Circulation: Cardiovascular Genetics 5*, 301. doi:10.1161/CIRCGENETICS.111.960872

Ma, L., Roman-Campos, D., Austin, E.D., Eyries, M., Sampson, K.S., Soubrier, F., Germain, M., Trégouët, D.-A., Borczuk, A., Rosenzweig, E.B. (2013). A Novel Channelopathy in Pulmonary Arterial Hypertension. *New England Journal of Medicine 369, 351*. doi:10.1056/NEJMoa1211097

Ousterout, D.G., Kabadi, A.M., Thakore, P.I., Majoros, W.H., Reddy, T.E., and Gersbach, C.A. (2015). Multiplex CRISPR/Cas9-Based Genome Editing for Correction of Dystrophin Mutations that Cause Duchenne Muscular Dystrophy. *Natural Communication 6*, 6244. doi:10.1038/ncomms7244

Peacock, A., Murphy, N., McMurray, J., Caballero, L., and Stewart, S. (2007). An Epidemiological Study of Pulmonary Arterial Hypertension. *The European Respiratory Journal 30*, 104–109. - PubMed - NCBI.

Saji, T. (2014). Clinical Characteristics of Pulmonary Arterial Hypertension Associated with Down Syndrome. *Pediatrics International 56*, 297–303. doi:10.1111/ped.12349

Sitbon, O., and Morrell, N. (2012). Pathways in Pulmonary Arterial Hypertension: The Future Is Here. *European Respiratory Review 21*, 321–327. doi:10.1183/09059180.00004812

Tonelli, A.R., Arelli, V., Minai, O.A., Newman, J., Bair, N., Heresi, G.A., and Dweik, R.A. (2013). Causes and Circumstances of Death in Pulmonary Arterial Hypertension. *American Journal of Respiratory Critical Care Medicine 188*, 365–369. doi:10.1164/rccm.201209-1640OC

Yotsukura, M., Miyagawa, M., Tsuya, T., Ishihara, T., and Ishikawa, K. (1988). Pulmonary Hypertension in Progressive Muscular Dystrophy of the Duchenne Type. *Japanese Circulation Journal 52*, 321–326.- PubMed - NCBI.

Zhou, G., Chen, T., and Raj, J.U. (2015). MicroRNAs in Pulmonary Arterial Hypertension. *American Journal of Respiratory Cell and Molecular Biology 52*, 139–151. doi:10.1165/rcmb.2014-0166TR