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Short Communication

Pulmonary Interstitial Glycogenosis and Congenital Heart Disease: Pathways in Fetal Cardio-Pulmonary Development

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Abstract

Pulmonary Interstitial Glycogenosis (PIG) is a rare condition of undetermined incidence of interstitial lung disease, with unique histologic features. The cellular and molecular mechanisms of this disease are not fully elucidated. The clinical findings of respiratory distress and hypoxemia are among the clinical features which can occur among infants with congenital heart disease (CHD). Methods: Electronic medical records (EMR) from the dates 8/1/2009 to 5/5/2016, using ICD (international classification of disease) codes corresponding to: i) Transposition of the Great Arteries (TGA), ii) Tetralogy of Fallot (TOF), iii) persistent pulmonary hypertension (PPH) and iv) pulmonary interstitial glycogenosis (PIG), were searched to identify cases of associated PIG and CHD or PPH. A literature search using PubMed/Medline from 2002 to 2016 was conducted to identify cases of CHD and PIG, and PPH and PIG. Results: The EMR search identified two cases of PIG, but none were associated with TGA or TOF. One of the two cases were associated with PPH. The literature search identified eight cases of PIG in association with CHD or PPH as described in seven articles. Conclusions: There is an association between PIG and cardio-vascular malformations. Overlapping molecular pathways involved in the developing cardio-vascular system and mesenchyme of the lung should be further studied. Among particular pathways suggested as the topic of future study include NOTCH and VEGF signaling pathways.

Keywords: *Congenital Heart Disease; Pulmonary Interstitial Glycogenosis; Neonatal; Infant; Interstitial Lung Disease*

Introduction

Pulmonary Interstitial Glycogenosis (PIG) is an idiopathic form of interstitial lung disease, identified primarily among neonates and young infants. The disorder has been associated with premature and aberrant lung growth and development, respiratory distress and congenital heart disease (CHD). The histopathology of the disease is characterized by increased glycogen laden mesenchymal cells in the alveolar interstitium, while sparing the alveolar spaces and lining 1 [1].

Deutsch., *et a*l. demonstrated that patchy PIG was present in association with vascular disorders in 22% of ILD cases 2 [2]. PIG is considered in the differential diagnosis when the degree of respiratory compromise could not be fully be fully explained by cardiac physiology.

This study was conducted with the aims to: 1) characterize the incidence of CHD associated with PIG, using a large database of CHD infants, 2) identify the association of PIG with persistent pulmonary hypertension, 3) review of current literature using the search terms of congenital cardiac disease and PIG and persistent pulmonary hypertension and PIG. The early recognition of this finding among infants with complex congenital heart disease, may lead to further understanding of the disease, fetal development and treatment. The association with persistent pulmonary hypertension should be further explored. The actual incidence of PIG may be higher, if PIG is included in the differential of neonatal respiratory distress. Currently, the actual incidence is not known.

Materials and Methods

Electronic Medical Records Search

The electronic medical records (EMR) database of a large pediatric urban medical center was searched to identify records from 8/1/2009 to 5/5/2016, using ICD (International Classification of Disease) codes for the diagnoses of: i) Transposition of the Great Arteries (TGA), ii) Tetralogy of Fallot (TOF), iii) persistent pulmonary hypertension (PPH). The ICD codes for each condition were used to identify the number of cases in the database during this time period. The search was conducted only using anonymized data. The specific complex cardiac diseases selected were based on pilot analysis of the database. These were ICD codes found within the EMR and available for further analysis.

The list of these cases was then searched to identify cases of PIG. The number of cases was then recorded for each condition identified individually and in co-existence (PIG and CHD, PIG and PPH). The CHD search selected these two CHD diagnoses for this study. Those infants with other CHD were not considered for the purposes of this study with focus on two of the more commonly identified CHD among neonates and infants. PIG tends to be diagnosed among young infants rather than older children with CHD. Records prior to this time period were not initially entered into the current EMR system of EPIC.

Literature Search

A literature search of the PubMed database was conducted from 2002 to May 2016 with search terms of Pediatric as defined by (0-18 years of age) and Pulmonary Interstitial Glycogenosis (PIG) and Congenital Heart Disease. Cases of CHD and PIG and PPH and PIG, were then identified from these articles. The exclusion criteria of adult published cases was used. The search was open and not structured further to exclude any cases identified (Figure 1).

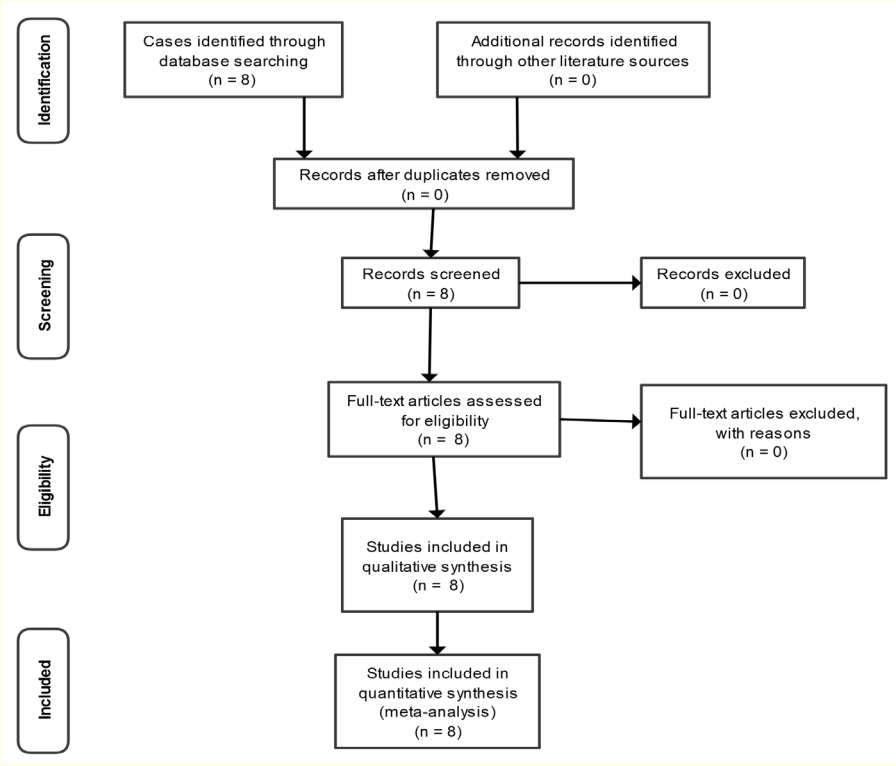

Figure 1: *PRISMA 2009 Flow Diagram.*

Additional literature was identified by reference lists from the identified articles and incorporated in the discussion section of the article.

Results

EMR search

There were 1,536,513 total individual cases/patients in the electronic database during the time period of 8/1/2009 to 5/5/2016.

The following number of patients with each disorder was identified as follows:
i) Transposition of the Great Arteries (TGA): n = 508
ii) Tetralogy of Fallot (TOF) n = 647
iii) Persistent Pulmonary Hypertension (PPH), n = 2.
iv) Pulmonary Glycogenosis (PIG) n = 2
v) PIG + CHD (i or ii) = 0
vi) PIG + PPH, n = 1

Literature Search

The literature search from PubMed identified a total of seven articles (Table 1). Among these articles, eight cases of vascular malformation, cardiac disease, pulmonary hypertension in association with PIG were identified. The cases were described by i) Gestational Age and ii) Cardiac lesion and anatomy/findings for purposes of analysis as shown in Table I, as available.

1	FT	Male	PPH, PDA	Bx + PIG	Steroids	No survival	Life 11 days
2	FT	Male	PPH, D-TGA, PDA	+PIG	Steroids	Survived	
3	FT	F	Extrapericardial AP window	+PIG	No Steroids	Survived	
4	34.5 week	Male	PS, redundant PV, RVH mild	+PIG	Post extub steroids	Survived	
5	FT	F	PDA, PFO, D TGA	+PIG	Steroids	Survived	
6	FT	Male	DORV, VSD, PS	+PIG	No steroids	Survived	
7	FT	Male	PFO, myopathy	+PIG	No steroids	No Survival	71 days
8	FT	NA	Hypoplastic Ao arch, PDA, PPH, mild Ao coarc	+PIG	Steroids	Survival	

Abbreviations

FT: Full Term; PPH: Persistent Pulmonary Hypertension; PDA: Patent Ductus Arteriosus; D-TGA: Dextro Transposition of the Great Arteries; PFO: Patent Foramen Ovale; PS: Pulmonic Stenosis; PV: Pulmonary Valve; RVH: Right Ventricular Hypertrophy

There was one case identified based on this search of a premature infant with pulmonary stenosis, redundant pulmonary valve, mild right ventricular hypertrophy. There were 6 infants born at term, and one without a specified gestational age. There were five cases of associated pulmonary hypertension and PIG. There were two cases of TGA and PIG. One child born with an extra pericardial AP window had a two vessel anomalous umbilical cord.

One of the articles found described a case of PIG and Noonan's syndrome in a premature infant. This case was also part of the EMR search results, since the patient was from the same center. Among the cases identified, there were two non-survivors, and one of the two infants had been treated with steroids. All patients were diagnosed by biopsy. There were 4 infants treated with steroids and 4 did not have a steroid treatment course for PIG.

Discussion

Pulmonary Interstitial Glycogenosis: Histopathology

This study identified cases of PIG in association with CHD and/or pulmonary hypertension. The association has not been previously

described in this manner. Based on the analysis, steroid treatment is not directly associated with survival, but in some cases, lead to improvement clinically. The gestational age of the infants indicated that PIG is not directly associated with premature delivery in the majority of cases identified. This study is limited by the analysis of retrospective data within publications, and relies on the information provided by the references. Since there are many forms of CHD, two in particular were chosen for study within the center. The literature search though included all CHD in association with PIG, future studies formally studying the dose and administration of steroids in a controlled trial would lend more information on management of PIG.

Pulmonary interstitial glycogenosis (PIG) is a form of infantile interstitial disease which is rare among infants and children born either prematurely or at term [3]. The pathophysiology of the disease is not fully characterized although the histopathologic finding of glycogen laden mesenchymal cells in the interstitium of the lung is one the hallmark features. The term of PIG, proposed by Canakis., et al. is based on the presence of uniform histologic features of thickened interstitium and abundant cytoplasmic glycogen sparing the alveolar spaces and lining [4]. In this description of three early cases of PIG, there were no cases of CHD in association. The authors described a striking abnormality of diffuse interstitial thickening in the absence of hyperplasia of alveolar lining cells or deposition in the alveolar space [4]. Among the unique findings, included, the finding of immature interstitial cells containing abundant cytoplasmic glycogen on samples processed for electron microscopy. The same authors concluded that PIG is rare and is a developmental, rather than inflammatory or reactive abnormality [4].

Congenital Heart Disease and Pulmonary Interstitial Glycogenosis (PIG)

The findings of this current study suggest that the end result of these pathognomonic histologic features can be found in association with congenital heart disease, pulmonary hypertension and vascular disease. The association remains rare, but this may be a result of a lack of histologic lung biopsy samples from CHD patients undergoing surgical repair. The actual incidence may be underestimated, due to a lack of histopathologic pulmonary biopsies in this population, but this is a topic of future study. Those infants with cardio-pulmonary physiology in association with prolonged hypoxemia and pulmonary hypertension not fully explained by CHD alone, should therefore be considered for lung biopsy based on these current findings and those previously reported [5]. An additional one case of PIG with significant cardiac findings was identified. King., et al. described a full term infant male with lung maturational arrest, large PDA and PFO. This case supports that there may be aberrant pathways in pulmonary vascular remodeling and PIG, associated with impaired lung maturation [6].

Proposed Molecular Mechanisms

The molecular basis for the hallmark histologic findings is not fully elucidated. Based on the rarely documented association between vascular and cardiac malformations and PIG, common cellular and molecular pathways should be considered.

During normal lung development, based on a rat fetal model, airway epithelial cells contained abundant glycogen deposits and lamellar bodies [7]. Type II pneumocytes which contain lamellar bodies contain significant amounts of glycogen. PIG in contrast, is an interstitial disease characterized by glycogen deposits, sparing the alveolar space. The process by which this occurs is still a subject of study and a future research directive.

Interestingly, in a study of hypoxia inducible factor (HIF) in an embryonic mouse lung model, a three point mutation in HIF conferred a lethal mutation associated with impaired epithelial maturation [8]. Decreased surfactant was associated with expanded glycogen pools in the pulmonary cells. In this study, there was a concomitant increase in VEGF A and C production and indirect inactivation of multiple NOTCH pathways in endothelial precursor cells [9].

The role of glycogen in the developing lung may include serving as a source of substrate for fatty acid synthesis, but cytoplasmic glycogen is not typically found in the normal fetal or post-natal interstitium [4]. Pathways of vascular and cardiac development in response

to in utero hypoxia should be conducted to further elucidate the process by which glycogen is deposited in the interstitium in PIG. Among specific pathways of interest, include NOTCH and growth factor pathways.

The NOTCH signaling pathway is involved in the modulation of three cardiac cellular processes relevant to the embryonic development of the cardio-vascular system in the fetus. Among these are: i) survival of cardiomyocytes, ii) cardiac stem cell differentiation and iii) angiogenesis. One example of the coordination between NOTCH and VEGF signaling occurs as new blood vessels are formed [10]. The activation of NOTCH normally results in VEGF activation, with downstream control in preventing neighboring cells from disrupting new vessel formation. In the presence of hypoxia, therefore it is proposed that this normal coordination does not occur in CHD and PIG. NOTCH signaling is important in epithelial-mesenchymal transition (EMT), and VEGF is similarly controlled in this process. Thus, mesenchymal interstitial glycogen deposits among CHD infants may be a result of aberration in these two particular pathways [11].

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Disclosures

The author has no conflict of interest and no disclosures.

Bibliography Addendum: Table I

There were seven articles found which described a total of eight cases.

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