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Echocardiographic Predictors of Alveolar Capillary Dysplasia: A Case-Control Study

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Abstract

Objective

To evaluate early echocardiographic variables of neonates with alveolar capillary dysplasia (ACD).

Study Design

A case-control study of five neonates with ACD and their matched controls on extracorporeal membrane oxygenation from 2000-2011. Two cardiologists prospectively reviewed first admission echocardiograms. Statistical tests included Kappa, T-test, Mann-Whitney, Fisher's exact, and Chi-square analysis.

Results

Excellent inter-rater reliability readings were achieved (Kappa 0.75-1). Tricuspid regurgitation (TR) velocities between the groups were not statistically significant; all ACD cases and 75% of the controls had TR velocities ≥ 3.2 m/sec. More ACD cases had moderate-severe TR jet (80% vs. none, $p<0.01$); moderate-severe right atrial enlargement (RAE) (100% vs. none, $p<0.01$); moderate-severe right ventricular (RV) dilatation (100% vs. none, $p<0.01$); and moderate-severely depressed RV function (60% vs. none, $p<0.01$). ACD patients were 12 times more likely to have a combination of moderate-severe RAE and moderate-severe TR jet compared to controls (OR = 11.6 [2-68]).

Conclusion

The combination of moderate-severe RAE and TR jet unresponsive to maximal interventions should alert clinicians of the possibility for ACD. We speculate that early echocardiographic predictors may identify at-risk neonates with fatal ACD and lead to early consideration of lung transplant.

Keywords: Alveolar capillary dysplasia; Persistent pulmonary hypertension of the newborn; Hypoxemic respiratory failure; Echocardiographic markers

Introduction

Neonatal alveolar capillary dysplasia (ACD), with misalignment of the pulmonary veins, is a rare, irreversible congenital lung disease characterized by severe persistent pulmonary hypertension of the newborn (PPHN) and refractory hypoxemia, unresponsive to maximal cardiorespiratory support [1]. ACD was first reported by MacMahon in 1947 when he described three term newborns who died within 48 hours after birth with a clinical diagnosis of "fetal atelectasis of unexplained cause" but later confirmed to have ACD by their post-mortem histologic pulmonary findings [2]. These newborns showed an arrest in normal alveolar development as illustrated by their "too few alveoli", "too much interstitial tissue", and "exaggerated demarcation of the lobules by abnormally wide interlobular septa" [2]. Similarly, Janney et al. in 1981 wrote about a patient "with the syndrome of persistent fetal circulation; morphologically, however, the patient was found to have a unique form of pulmonary dysplasia" [3]. In 2004, de Mello further described ACD as "a lethal disorder in human neonates in whom there is a failure of formation of alveolar capillaries with a consequent absence of formation of the normal air-blood barriers" [4].

In the first postnatal week, clinical and routine laboratory markers differentiating ACD from reversible causes of severe pulmonary hypertension are poorly defined [1]. In neonates, the initial presentation of respiratory failure due to ACD is not significantly different from other disease processes with severe PPHN [1]. These manifestations of pulmonary hypertension such as presence of respiratory distress, generalized cyanosis, severe hypoxemia, and significant hypotension immediately after birth and into the first week of postnatal life may present similarly, without specifically pointing to an underlying cause. If distinct early markers for ACD could be determined, consideration of lung transplant in the first postnatal week may provide hope for survival for this otherwise lethal condition.

Our study aimed to identify at-risk neonates for fatal ACD during the first postnatal week using early non-invasive echocardiographic markers. We hypothesized that patients with ACD have specific echocardiographic variables consistent with significant right-sided cardiac pressure elevations in the first postnatal week of life secondary to the fixed higher pulmonary vascular resistance that developed early while still in utero, unique from other causes of reversible pulmonary hypertension.

Design/Methods

Subjects

This retrospective case-control study at the quaternary-care neonatal intensive care unit of Children's Hospital Los Angeles was conducted from January 2000 to May 2011. Each ACD case was matched to one control. Lung biopsies were not performed for any of the patients. Diagnosis of ACD was confirmed at autopsy for all cases.

Inclusion criteria for the selection of controls included a diagnosis of meconium aspiration syndrome (MAS) and sepsis with pulmonary hypertension admitted within one to two years for each matched case. Controls were matched on the basis of gestational age (37 to 42 weeks), birth weight (2500 – 4000 g), treatment with inhaled nitric oxide, and extracorporeal membrane oxygenation (ECMO) support. Diseases associated with pulmonary hypoplasia, such as congenital diaphragmatic hernia, were excluded from the control group. Also, a control with a final diagnosis of idiopathic pulmonary hypertension was excluded as it may actually have been ACD, especially if autopsy was not performed.

All cases and controls were treated with inhaled nitric oxide and supported on ECMO. Inhaled nitric oxide was administered in neonates with supra-systemic pulmonary artery pressures seen on echocardiography and a post-ductal partial pressure of oxygen in arterial blood (PaO_2) of less than 80 mm Hg on 100% fraction of inspired oxygen (FiO_2) despite optimal lung inflation. ECMO was provided when a patient had an oxygenation index (OI) (mean airway pressure [MAP] x FiO_2 / PaO_2) greater than 40 for a four-hour period despite inhaled nitric oxide administration, optimal lung inflation, and effective cardiovascular support.

Data Collection

Variables collected from the medical records included patient demographics, onset of illness, presence of congenital anomalies, admission arterial blood gas pH and partial pressure of carbon dioxide in arterial blood ($PaCO_2$), admission MAP, and pre-ECMO OI.

The first admission echocardiograms for ACD cases and controls were obtained and prospectively reviewed by two independent cardiologists, who were blinded to the identity of the cases and controls. All of the patients in the study were already being treated with inhaled nitric oxide at the time of the first admission echocardiogram, but not yet on ECMO support. The cardiologists independently evaluated the following echocardiographic variables: 1) tricuspid regurgitation (TR) velocity (m/sec), 2) TR jet grading (trivial, mild, moderate, or severe), 3) presence of PDA and direction of flow, 4) interventricular septum (normal, flat, or bowing to the left), 5) right ventricular (RV) size (normal or mild, moderate, or severe dilatation, 6) presence of right ventricular hypertrophy (RVH), 7) RV function (mild, moderate, or severely depressed), 8) right atrial enlargement (RAE) (absent, mild, moderate, or severe), and 9) presence of pulmonary insufficiency (PI) (physiologic, mild, moderate, or severe).

The cardiologists assessed TR grading based on the width of the TR jet area (Figures 1 and 2). The TR velocities described in Table 3 were designated as moderately elevated at ≥ 3.2 m/sec and severely elevated at ≥ 3.9 m/sec. These arbitrary cut-offs were based on the fact that the pulmonary systolic pressures during the early postnatal age are normally around 30 mmHg. Therefore, using Bernoulli equation, a TR jet velocity of 3.2 m/s would correspond to a moderately elevated pressure gradient of 41 mmHg, while a TR jet velocity of 3.9 m/s would correspond to a severely elevated pressure gradient of 61 mmHg.

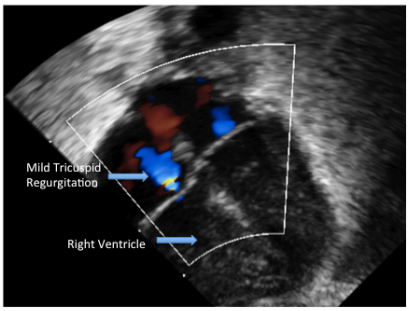

Figure 1: Mild Tricuspid Regurgitation Jet
An echocardiographic image (seen on apical four-chamber view) of one of our patients with mild tricuspid regurgitation jet

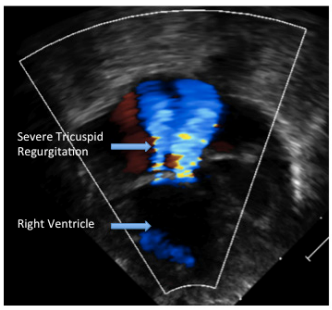

Figure 2: Severe Tricuspid Regurgitation Jet
An echocardiographic image (seen on apical four-chamber view) of one of our patients with severe tricuspid regurgitation jet. Note presence of wide tricuspid regurgitation jet that extends towards posterior wall of right atrium

Table 3 Echocardiographic Variables

Echocardiographic variables measuring the degree of pulmonary hypertension and presence of intracardiac shunts between ACD cases and controls.

Echocardiographic Variables	ACD Cases	Controls	p Value
TR velocity ≥ 3.2 m/sec	5 / 5 (100%)	3 / 4 (75%)	0.89
TR velocity ≥ 3.9 m/sec	4 / 5 (80%)	1 / 4 (25%)	0.10
TR jet grading, moderate to severe	4 / 5 (80%)	0 / 5 (0%)	0.01
PDA flow, R to L	2 / 5 (40%)	0 / 3 (0%)	0.21
Septal bowing to left	2 / 5 (40%)	0 / 5 (0%)	0.11
RV size, moderate to severe dilatation	5 / 5 (100%)	0 / 4 (0%)	0.003
RVH	3 / 3 (100%)	2 / 3 (67%)	0.27
RV function, moderately to severely depressed	3 / 5 (60%)	0 / 5 (0%)	0.04
RAE	5 / 5 (100%)	0 / 5 (0%)	0.002
PI, mild to severe	4 / 5 (80%)	1 / 5 (20%)	0.06

TR = Tricuspid regurgitation
PDA = Patent ductus arteriosus
R to L = Right to left
RV = Right ventricle
RAE = Right atrial enlargement
PI = Pulmonary insufficiency

*Due to echocardiogram data storage issues affecting the study period, some of the echocardiogram images were not retrieved by the cardiologists, but statistical analyses were employed to all of the available data.

The RV size was examined in comparison to the left ventricle, while RAE was graded in comparison to the left atrium (Figures 3 and 4). Moreover, the RAE described in Table 3 was measured by assessment of the right atrial minor axis dimension and qualitatively compared to the left atrial minor axis dimension in the apical four-chamber view [5].

This study was approved by the Institutional Review Board (IRB) at Children's Hospital Los Angeles.

Statistical Analysis

Distribution of continuous variables was tested for normality. Equality of means was analyzed by T-test for normally distributed variables, while equality of distribution was analyzed by Mann-Whitney test. Distribution and proportions of patients in each group were compared by using the Fisher's exact test. Chi-square analysis was employed for categorical variables and continuous variables that were recorded into ordinal measures. A p value of < 0.05 was considered statistically significant.

Inter-rater reliability readings of the echocardiograms between the two cardiologists who prospectively reviewed the images of all first admission echocardiograms were measured using Kappa statistics. Kappa calculation is a measure of how much agreement is present between two or more independent observers analyzing the same variables. Scores can range from -1 to +1; a perfect agreement between the two independent observers is a score of 1, a score of 0 would denote an agreement expected by chance, while negative values would denote agreements that are worse than if they occurred by chance alone.

Analyses were performed using Stata/SE 10.0 software (Stata Corporation, College Station, TX, USA).

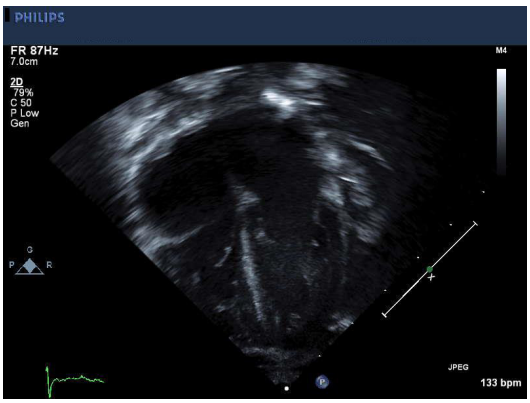

Figure 3: Mild Right Ventricular Dilatation
An echocardiographic image (seen on apical four-chamber view) with mild right ventricular dilatation

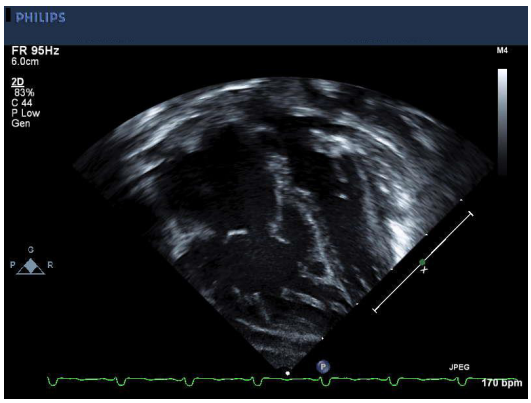

Figure 4: Severe Right Ventricular Dilatation
An echocardiographic image (seen on apical four-chamber view) with severe right ventricular dilatation. Note the larger size of right ventricle in comparison to left ventricle

Results

Five neonates with ACD confirmed by autopsy were matched to five controls with meconium aspiration syndrome and sepsis with pulmonary hypertension. All patients in the study were treated with inhaled nitric oxide for pulmonary hypertension and subsequently supported with ECMO. Demographic variables demonstrated a larger proportion of males in the ACD group (80% vs. 40%). There were no statistical differences for the mean birth weights (3165 g ± 313 vs. 3255 g ± 419) and gestational ages at birth (39.9 ± 1.0 vs. 39.9 ± 1.1) between ACD cases and controls (Table 1).

Compared to controls, ACD cases had slightly (but insignificantly) higher Apgar scores at 1 and 5 minutes, respectively. Furthermore, 60% of ACD cases had their onset of respiratory distress within first hour of life, as compared to 100% of the controls (Table 1).

Table 1: Demographic, Clinical, and Admission Respiratory Variables
Demographic, selected clinical, and admission respiratory variables obtained between ACD cases and controls

Variables	ACD Cases (N = 5)	Controls (N = 5)	p Value
Males (%)	80	40	0.20
BW (grams)	3165 ± 313	3255 ± 419	0.71
Gestation at birth (weeks)	39.9 ± 1.0	39.9 ± 1.1	0.94
Apgar, 1 minute	7 ± 2	5 ± 2	0.06
Apgar, 5 minutes	9 ± 1	6 ± 3	0.12
Presence of symptoms* within first hour of life	3 / 5 (60%)	5 / 5 (100%)	0.29
Survival to discharge	0 / 5 (0%)	5 / 5 (100%)	0.002
Admission pH	7.42 ± 0.1	7.30 ± 0.2	0.28
Admission pCO_2	39.6 ± 23.1	53.2 ± 28.1	0.43
Admission MAP (cm H_2O)	14.5 ± 2.6	16.7 ± 2.9	0.24
Pre-ECMO OI	44.4 ± 13.9	40.2 ± 19.4	0.71

*presence of at least one of the following: poor respiratory effort, cyanosis, retractions, desaturation, or hypotension

MAP = Mean Airway Pressure
OI = Oxygenation Index = mean airway pressure (MAP) x fraction of inspired oxygen (FiO_2) / post-ductal partial pressure of oxygen in arterial blood (PaO_2)

Data expressed as mean ± standard deviation

More ACD cases than controls were found to have associated gastrointestinal (40% vs. 0%) and genitourinary (20% vs. 0%) anomalies. In one ACD patient, multiple gastrointestinal and genitourinary anomalies were seen, specifically, Hirschsprung disease, small intestine with submucosal lymphangiectasia and mild congestion, bilateral hydronephrosis, bilateral hydroureter, and enlarged urinary bladder. Another ACD case was found to have an annular pancreas, splenomegaly, and hepatomegaly with dysplastic portal triads. None of the ACD cases had any dysmorphic features documented on physical exam.

Although not statistically significant, the mean admission arterial pH for the ACD group was higher (7.42 ± 0.1 vs. 7.30 ± 0.2) than the control group; while the mean arterial pCO2 (39.6 ± 23.1 vs. 53.2 ± 28.1) and mean airway pressure (14.5 ± 2.6 vs. 16.7 ± 2.9) were both lower for the ACD cases (Table 1).

Agreements between the two cardiologists, as assessed by Kappa inter-rater reliability for all echocardiographic measurements, were greater than or equal to 0.75, and therefore, interpreted as excellent percent agreement beyond chance.

There was no statistical difference in the degree of tricuspid regurgitation (TR) velocities between the two groups. All ACD cases and 75% of the controls had TR velocities ≥ 3.2 m/sec (Table 2). Though in comparison to the controls, there was a qualitative difference in that a greater proportion of ACD cases had moderate to severe tricuspid jet regurgitation grading (80% vs. 0%, p<0.01); moderate to severe RAE (100% vs. 0%, p<0.01); moderate to severe RV dilatation (100% vs. 0%, p<0.01); and moderately to severely depressed RV function (60% vs. 0%, p 0.04). Furthermore, using logistic regression analysis, ACD patients were 12 times more likely to have a combination of moderate to severe RAE and moderate to severe tricuspid jet regurgitation compared to controls (odds ration [OR] = 11.6 [2-68]).

All patients with ACD expired, with a life span that ranged from 16 to 95 days. In comparison, all controls survived to discharge.

Table 2: Echocardiographic Variables

Echocardiographic variables measuring the degree of pulmonary hypertension and presence of intracardiac shunts between ACD cases and controls

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*Due to echocardiogram data storage issues affecting the study period, some of the echocardiogram images were not retrieved by the cardiologists, but statistical analyses were employed to all of the available data.

Discussion

Congenital alveolar capillary dysplasia (ACD), with misalignment of the pulmonary veins is considered a rare and lethal condition in neonates, which was first characterized by Dr. MacMahon in 1947 as "a defective and hypoplastic development of pulmonary alveoli" [2]. Almost 70 years later, close to only 200 ACD case reports worldwide have been published [1,6-12]. The rarity of this disease was paralleled in our study as our quaternary center only identified five ACD cases in a span of 11 years (2000-2011). Nevertheless, the prevalence of ACD worldwide may actually be higher as it is very likely that many ACD cases without biopsy or postmortem examinations may have been classified as severe pulmonary hypertension of unknown etiology. Since no clinical markers have been able to reliably distinguish ACD from other causes of neonatal pulmonary hypertension, ACD should be considered early in newborns and infants presenting with severe pulmonary hypertension and refractory hypoxemic respiratory failure [1,13].

Early differentiation of neonates with fatal ACD from reversible causes of pulmonary hypertension remains difficult and specific clinical markers are lacking. Our study is the first to examine the potential role of early echocardiographic markers associated with the severe neonatal form of ACD

in the first postnatal week. In our study, we have shown that significantly higher right-sided cardiac pressures and right-sided chamber enlargements could be associated with ACD. Specifically, the presence of combined moderate to severe right atrial enlargement and moderate to severe tricuspid regurgitation jet regurgitation grading are highly predictive of ACD. Presence of these unique early right-sided echocardiographic markers for ACD during the first postnatal week, despite aggressive and optimal support may heighten the level of suspicion for ACD. Consequently, clinicians may be prompted to immediately confirm the disease and refer for lung transplant evaluation.

Unfortunately, neonates with severe pulmonary hypertension secondary to reversible and irreversible causes can present with similar signs and symptoms including tachypnea, cyanosis, severe hypoxemia, right ventricular failure, systemic hypotension, and metabolic acidosis. In addition to right ventricular failure seen in patients with severe pulmonary hypertension, most if not all ACD cases present with disproportionate moderate to severe right atrial enlargement as compared to newborns and infants with reversible pulmonary hypertension not affected by ACD. The pathognomonic findings of severe and fixed pulmonary hypertension attributed to "the deranged vascular endothelial growth factor signaling" have been previously described in ACD patients [14]. Furthermore, despite the presence of severe pulmonary hypertension and profound hypoxemia, neonates with ACD can be differentiated from others by relative initial sparing of lung parenchymal disease as exhibited by their relatively normal lung mechanics and compliance [1]. In general, neonates with ACD tolerate conventional mode of mechanical ventilation with tidal volumes appropriate for their gestational age. In our study, it is interesting to point out that our ACD cases had a trend towards lower $PaCO_2$ and lower MAP at the time of presentation, consistent with the required mechanical ventilation needs as assessed by the relative sparing of lung parenchymal disease described in the ACD patient population.

In general, the initial management of newborns and neonates with ACD is similar to those with reversible forms of severe pulmonary hypertension. These patients should be provided respiratory support to target optimal lung inflation and therapies that promote pulmonary vascular dilatation, including oxygen and inhaled nitric oxide. In selected cases the role of prostacyclin, phosphodiesterase inihibitors (e.g. milrinone and sildenafil), and cardiopulmonary bypass with ECMO should be carefully assessed. The expected responses to these therapies may serve and enable clinicians to distinguish neonates with ACD from reversible forms of severe pulmonary hypertension. In patients with pulmonary hypertension secondary to sepsis, pneumonia, or meconium aspiration syndrome significant improvement and attenuation of pulmonary hypertension with optimal respiratory support and pulmonary vascular modulators is generally achieved within the first week of treatment. In contrast, administration of these interventions may afford only transient improvement in patients with ACD, followed by a continued clinical deterioration. It has been shown that even with increasing concentrations of inhaled nitric oxide [15,16] and cardiopulmonary support with ECMO [17], mortality rates for ACD patients have not altered. Unfortunately as a consequence of our lack of early differentiating clinical markers, ACD is often not considered until patients are beyond their first postnatal week, and most often by then these patients exhibit multi-organ failure due to persistent hypoxemia. In some centers, cardiac catheterization may provide further clinical indices to delineate the etiology of pulmonary hypertension, wherein findings of "an elevated right ventricular filling pressure in the presence of normal pulmonary venous return and a diminished or absent capillary blush phase" has been described in ACD patients [18]. Ultimately, the definitive diagnosis for ACD must rely on histopathology of lung tissue demonstrating the characteristic features of decreased number of capillaries, thickened alveolar septa, and medial hyperplasia of small pulmonary arteries, either via lung biopsy or autopsy [19,20].

Few groups have reported proceeding to lung biopsy for confirmatory diagnosis, but performing open lung biopsy while on ECMO is still rarely done [21,22]. Possibly, with the help of our echocardiographic predictors for ACD, suspicion for a lethal disease may be raised earlier and will enable more centers to consider a confirmatory biopsy sooner.

Our findings may add to a stepwise approach in management of patients with severe and refractory PPHN with associated hypoxemic respiratory failure. Patients who have significantly elevated right atrial and right ventricular pressures despite attempt to modulate their pulmonary vascular tone in the first postnatal week should be referred to centers with expertise in the evaluation for ACD. Early identification of ACD cases could be sought when the presence of elevated right-sided cardiac pressures on echocardiography is present despite optimization of conventional medical therapy. Furthermore, genetic evaluation for known genes associated with development of the lung and its vasculature should be concomitantly undertaken, as the FOXF1 gene mutation may be found in up to 40% of patients with ACD [19,23]. Early confirmation of ACD by clinical, genetic, and histopathologic means can enable clinicians and families to discuss all possible options including the potential for referral to a lung transplant center or to proceed with palliative care.

We acknowledge that the findings in our study were limited to a single center. However, it involved a multidisciplinary team in a quaternary referral center, experienced in irreversible pulmonary dysplasias, such as ACD. Our team is comprised of neonatologists, pulmonologists, cardiologists, transplant surgeons, ethicists, and palliative care specialists. It is also relevant for clinicians to appreciate that the presence of elevated right-sided cardiac pressures and right-sided chamber enlargements do not specifically point to ACD without performing confirmatory histopathological testing. The combination of moderate to severe right atrial enlargement and tricuspid jet regurgitation unresponsive to maximal cardiorespiratory support should alert clinicians of the possibility for ACD. We speculate that these unique early echocardiographic characteristics consistent with significantly elevated right-sided cardiac pressures may identify at-risk neonates for fatal ACD in the first postnatal week, which may lead to earlier enlistment for lung transplant or avoidance of futile, expensive interventions.

Conflicts of Interest

All authors have declared no conflicts of interest.

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