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Late onset of pulmonary hypertension and sepsis in omphalocele infants

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Abstract

A subset of omphalocele infants has respiratory decompensation after the first week of life and PHN is diagnosed. Infection may initiate decompensation. In some, PHN is distinct from pulmonary hypoplasia as they oxygenate on room air for some time after birth. With aggressive treatment and follow-up, PHN can resolve. The late diagnosis of PHN in infants with omphalocele is previously unappreciated and deserves further study.

1. Materials and methods

After Institutional Review Board approval, a retrospective review was performed of 115 infants born with omphalocele at two academic children’s hospitals between 2000 and 2011. Fifty-eight were excluded because an echocardiogram was performed on the first day of life, during the phase of transitional circulation. No other echocardiograms were performed in these 58. In 51, PHN was diagnosed between day of life two and seven and they were excluded. The six included infants had a diagnosis of PHN after the first week of life.

Infant demographic data, cardiopulmonary status at birth, clinical deterioration, laboratory septic markers, culture data, B-type natriuretic peptide (BNP) levels, transthoracic echocardiograms, and clinical outcomes were recorded. Prenatal ultrasound and magnetic resonance imaging (MRI) reports were sought in the medical records.

The initial preoperative transthoracic echocardiograms were obtained. After recording the initial reports, a single cardiologist interpreted each one in blinded fashion, to eliminate reviewer variability in the diagnosis of PHN. Pulmonary hypertension was defined as flattening of the inter-ventricular septum during systole and/or a tricuspid regurgitant jet (TR) with an estimated right ventricular pressure greater than 40 mmHg when observed in the setting of hypoxemia [6]. The omphalocele defect was

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defined as a giant defect when 75% of the liver was visible in the sac [1].

A search of the published literature pertaining to omphalocele and pulmonary hypertension was performed using the PubMed online database. The language was limited to English, but year of publication was not limited.

2. Results

Demographic data are presented in Table 1. There were three females and three males born between 35 and 39 weeks gestational age. The median gestational age was 37.5 weeks, the median birth weight was 2502 g and the median weight/length z-score was 0.53. All were prenatally diagnosed by ultrasound and four met the criteria for giant omphalocele. None had prenatal MRI imaging available for review. All had normal chromosomal studies and no evidence of aneuploidy.

Infant cardiopulmonary data at birth and during the first week of life are presented in Table 2. All six infants maintained an oxygen saturation of 100% on the first day of life. Three were breathing room air. Three required intubation at birth and conventional mechanical ventilation. The sixth infant was extubated and breathing room air between DOL 3 and 15.

Three infants required no cardiopulmonary support at birth and nippled their feeds between day of life three and six. Three infants that required ventilator support at birth, tolerated gavage or nasojejunal (NJ) feeds between day of life 2 and 46. Infants one and three were diagnosed with Fryn and Goltz Syndrome, respectively.

Four had a transthoracic echo on day of life two and two on day of life three. All were initially diagnosed as having no pulmonary hypertension. A blinded retrospective review of the initial echocardiogram tapes by one cardiologist for this series, found subtle signs of PHN in four infants (Table 2). All congenital heart defects were simple, non-ductal dependent anomalies without hemodynamic significance.

Cardiopulmonary function deteriorated in all six infants (Table 3). Further investigations, imaging and treatment proceeded according to clinician specific practice. All six infants had laboratory studies consistent with infection from culture proven sepsis, bacteremia or pneumonia, on the day of deterioration.

Transthoracic echocardiography was performed between DOL 9 and 52 (median: DOL 15), and revealed PHN in all six. One underwent computed tomography angiography (CT-angio) on DOL 20. The fourth infant deteriorated with sepsis in the second week of life, and the PHN persisted. This was appreciated when she underwent a CT angio and cardiac catheterization (cath) on DOL 117 and was found to have severe PHN. The CT angio revealed a structurally normal heart in each infant.

Treatment of sepsis was broad spectrum antibiotics in all six cases which was subsequently guided by available culture results. Treatment of PHN in all six included nitric oxide, sildenafil, inotropes (dopamine and dobutamine) and milrinone (Table 3). All infants received paralytics with vecuronium and sedation with narcotics and versed to promote better ventilation during escalation of treatment. The results of any BNP levels were sought in the medical records, but none were obtained. The third infant received Esmolol for supraventricular tachycardia (SVT) that may respond to oxygenation and sepsis treatment. Within 24 h, the infant developed circuit disseminated intravascular coagulation with platelet consumption, combined with clots in the right atrial side of the circuit. A complete circuit change was done. Serial echocardiograms revealed worsening PHN, and clots in the right ventricle extending through the tricuspid valve. Due to worsening PHN and ECMO complications, a recommendation was made to withdraw care and the infant died on the third day of ECMO support (DOL 18).

Follow-up for three survivors ranged from 540 to 1219 days with a median of 868 days. Follow-up echocardiograms revealed the PHN resolved for all three. Two infants have tracheostomies and require support for chronic respiratory insufficiency. Infants 3 and 4 have mild neurologic impairment.

Infant 3 underwent a primary omphalocele repair on DOL 38. One week after repair, the infant returned to the operating room for a bowel obstruction with perforation. The infant required a bowel resection, but recovered and was discharged from hospital on DOL 59. There was no clinically significant PHN at this time. Sildenafil was discontinued before discharge.

Prior to discharge, this infant was diagnosed by skin biopsy with Goltz syndrome, a craniofacial syndrome (facial dermal hypoplasia). The infant had a cleft lip, a club foot and syndactyly. A brain MRI revealed mild frontal/temporal lobe atrophy, and bilateral optic

Table 1
Demographics of six infants with omphalocele and a late diagnosis of PHN.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Gestational age (weeks)</th>
<th>Birth weight (g)</th>
<th>Weight/length z-score at birth</th>
<th>Inborn</th>
<th>Giant defect</th>
<th>Age at diagnosis by prenatal US (weeks)</th>
<th>Prenatal US report, omphalocele contents and heart evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>35</td>
<td>2644</td>
<td>0.53</td>
<td>No</td>
<td>No</td>
<td>16</td>
<td>Small bowel, hydroprophosis, two vessel cord, ASD</td>
</tr>
<tr>
<td>M</td>
<td>39</td>
<td>3775</td>
<td>0.55</td>
<td>Yes</td>
<td>Yes</td>
<td>18</td>
<td>Liver, small bowel, stomach, polyhydramnios, normal heart</td>
</tr>
<tr>
<td>F</td>
<td>39</td>
<td>2325</td>
<td>-0.28</td>
<td>No</td>
<td>No</td>
<td>20</td>
<td>Small bowel, small VSD</td>
</tr>
<tr>
<td>F</td>
<td>37</td>
<td>2448</td>
<td>-1.5</td>
<td>Yes</td>
<td>Yes</td>
<td>22</td>
<td>Liver, large and small bowel, hydronephrosis, oligohydramnios, Prominent Right atrium</td>
</tr>
<tr>
<td>M</td>
<td>35</td>
<td>2555</td>
<td>0.75</td>
<td>No</td>
<td>Yes</td>
<td>20</td>
<td>Liver, large and small bowel, small ASD</td>
</tr>
<tr>
<td>M</td>
<td>38</td>
<td>2299</td>
<td>0.53</td>
<td>Yes</td>
<td>No</td>
<td>12</td>
<td>Liver, small bowel, stomach, normal heart</td>
</tr>
</tbody>
</table>
nerve hypoplasia, but normal spectroscopy. Her initial EEG was abnormal. She failed her hearing test due to conductive hearing loss in the left ear. She required a gastrostomy tube for feeding. She was followed by neurology every three months and attended early physiotherapy and speech therapy.

At 19 months, she was walking with assistance, eating independently with a spoon and speaking several words. Her follow-up EEG was normal. At 10 years she attended regular school and had mild cognitive, motor, speech and hearing deficits. She has no respiratory difficulties.

Infant 4 has a giant omphalocele and repair is pending. This infant was diagnosed with PHN on ECHO at DOL 13 when she deteriorated with sepsis, and underwent tracheostomy for chronic lung disease at DOL 71. However, her persistent PHN was better appreciated by clinicians after she underwent cardiac catheterization at DOL 171. At the time of catheterization, she required 100% Fi02 and nitric oxide at 20 ppm. Her prognosis was considered very poor and her status was “do not resuscitate.”

After the catheterization confirmed severe PHN, she began long-term sildenafil and Bosentan therapy. By ten months, her Fi02 decreased to 25% and nitric oxide was discontinued. Serial echocardiograms guided the weaning of sildenafil. She was discharged to a chronic care facility at 10 months. At 2 years of age, after the PHN had improved, she underwent an open left thoracic CDH repair for a previously undiagnosed CDH and recovered well. At 3 years, she has mild PHN on echocardiogram, her Fi02 is 21% and she continues to take sildenafil. Her Bosentan was discontinued. Her pulmonary function studies are consistent with restrictive lung disease.

At 10 months of age, before hospital discharge, this infant underwent a brain MRI which revealed hypoxic ischemic encephalopathy (HIE). She required full gastrostomy tube feeds, had motor, cognitive and speech delays, and could sit with assistance, but appeared to track and hear normally. She was followed by neurology every 3 months and received physio and speech therapy. By 2 years, she was walking with assistance, and has only mild gross motor and cognitive delays.

Infant 5 underwent staged repair with complete closure of the omphalocele on DOL 151 and no other operations were performed. Sildenafil was discontinued before discharge. The child was discharged with a tracheostomy but no further long-term follow-up neurologic or respiratory evaluations were available.

## 3. Discussion

Respiratory insufficiency is a known complication in infants with an omphalocele, but the causes are not well understood [1]. Omphalocele infants with MR imaging-based observed/expected total fetal lung volumes (O/E TFLV) below 50% have significantly lower Apgar scores and prolonged ventilation [7]. This finding is

### Table 2

<table>
<thead>
<tr>
<th>Infant</th>
<th>Apgar 1 min</th>
<th>Apgar 5 min</th>
<th>Intubated at birth</th>
<th>Fi02 at birth (%)</th>
<th>Initial echo report</th>
<th>Blinded echo review</th>
<th>Echo: CHD</th>
<th>DOL 1st feeding</th>
<th>Genetic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>8</td>
<td>8</td>
<td>No</td>
<td>21</td>
<td>No PHN</td>
<td>Mild PHN</td>
<td>Dextrocardia</td>
<td>3</td>
<td>Fryn syndrome</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>9</td>
<td>No</td>
<td>21</td>
<td>No PHN</td>
<td>Mild PHN</td>
<td>No PHN</td>
<td>3</td>
<td>Goltz syndrome with cleft lip</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>Yes</td>
<td>Conv vent 55</td>
<td>No PHN</td>
<td>No PHN</td>
<td>Mild PHN</td>
<td>Normal</td>
<td>46 (NJ feed)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>Yes</td>
<td>Conv vent 40</td>
<td>No PHN</td>
<td>No PHN</td>
<td>Small ASD</td>
<td>Small VSD</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>Yes</td>
<td>Conv vent 30 Ext*</td>
<td>No PHN</td>
<td>No PHN</td>
<td>Mild PHN</td>
<td>Small PFO</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

* Infants 1–3 breathed room air at birth.
* Extubated.
* Infants 1–3 nipped feedings.

### Table 3

<table>
<thead>
<tr>
<th>Intubated DOL</th>
<th>Fi02*</th>
<th>ECHO DOL</th>
<th>Blood gas: base excess</th>
<th>Culture result</th>
<th>WBC/CRP</th>
<th>Vent (days)</th>
<th>Inotropes (days)</th>
<th>Milrinone and other (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12*</td>
<td>40</td>
<td>18</td>
<td>−4</td>
<td>Urine Enterobacter Blood Methicillin resistant Staph Blood Coagulase negative Staph</td>
<td>11/4</td>
<td>10</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>55</td>
<td>9</td>
<td>−5</td>
<td>Blood Coagulase negative Staph Trachea Staph aureus (pneumonia)</td>
<td>19/20</td>
<td>6</td>
<td>4</td>
<td>Esmolol SVT* on DOL 15</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>15</td>
<td>−3</td>
<td>Trachea, Staph aureus (pneumonia)</td>
<td>12/17</td>
<td>868 (trach DOL 71)</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Intubated at birth</td>
<td>HFOV 60</td>
<td>13</td>
<td>−9</td>
<td>Trachea, Staph aureus (pneumonia)</td>
<td>19/16</td>
<td>200 (trach DOL 52)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Intubated at birth</td>
<td>HFOV 65</td>
<td>52</td>
<td>−5</td>
<td>Blood Coagulase negative Staph Trachea Group B Strep (pneumonia)</td>
<td>18/18.4</td>
<td>4 (V-V ECMO)</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

* Infants 1–3 placed on conventional ventilation.
* CT Angio on DOL 20.
* CT Angio and Cardiac Cath on DOL 117.
* Supraventricular tachycardia
considered predictive of increased postnatal morbidity in omphalocele infants. These measurements represent incomplete lung development (pulmonary hypoplasia) which may contribute to locele infants. These measurements represent incomplete lung development (pulmonary hypoplasia) which may contribute to PHN in omphalocele infants. Recent data has suggested pulmonary hypertension (PHN) occurs with non-giant omphaloceles merits further investigation.

Table 4
Outcomes and day of life (DOL) follow-up (F/U) evaluation.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DOL F/U</th>
<th>Last echo DOL</th>
<th>Medication respiratory status</th>
<th>Neurologic status at hospital d/c (MRI results)</th>
<th>Omphalocele Repairs</th>
<th>Feeding status at F/U</th>
<th>Other operations DOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>22</td>
<td>PHN</td>
<td>Fi02 100%</td>
<td>Not repaired</td>
<td>NPO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>51</td>
<td>PHN</td>
<td>Fi02 100%</td>
<td>Not repaired</td>
<td>NPO</td>
<td>Sac rupture-debrided</td>
<td>46</td>
</tr>
<tr>
<td>Alive</td>
<td>1219</td>
<td>No PHN</td>
<td>Room air</td>
<td>Primary and G-tube</td>
<td>Full G-tube feeds</td>
<td>SBO,® malrotation, perforation</td>
<td>45</td>
</tr>
<tr>
<td>Alive</td>
<td>868</td>
<td>No PHN</td>
<td>Sildenafil Fi02 25%</td>
<td>Frontal lobe atrophy</td>
<td>Motor and cognitive delay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>540</td>
<td>No PHN</td>
<td>No meds</td>
<td>Not repaired</td>
<td>Full NJ feeds</td>
<td>Left CDH,® repair</td>
<td>800</td>
</tr>
<tr>
<td>Died</td>
<td>18</td>
<td>PHN</td>
<td>V-V ECMO</td>
<td>Staged</td>
<td>Nippling full feeds</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Hypoxic ischemic encephalopathy (HIE).
b Small bowel obstruction (SBO).
c Congenital diaphragmatic hernia (CDH).

One infant died after three days of veno-venous ECMO support at sixteen days of age. Review of the ELSO database revealed only eleven infants with omphalocele was placed on ECMO, all for PHN, and all since 2011 [13]. Veno-arterial ECMO was used for all but one, and seven (64%) were weaned from ECMO, but only two (18%) survived to discharge. Four of eleven in the ELSO series had a CDH in addition to an omphalocele. One infant in this series had omphalocele, severe PHN and a late-diagnosed CDH. Multiple factors may influence the developing lung and etiology of PHN.

Pulmonary hypertension is more commonly reported in giant omphalocele infants [5]. However, three infants in this series met the definition of non-giant omphalocele and one died. In a recent series, 28 omphalocele infants had PHN but only 17 (61%) met the definition of a giant defect, 11 (39%) were diagnosed with PHN by strict criteria, and had a non-giant omphalocele [4]. The fact that PHN occurs with non-giant omphaloceles merits further investigation.

The association of PHN with mortality in omphalocele infants is only recently appreciated. Associations for both PHN and omphalocele, and PHN and sepsis, are reported [4,5,8]. When these combined diagnoses exist, PHN should be sought and treated. Echocardiography should be performed after the second day of life, to allow resolution of the transitional circulation, and repeated if respiratory status worsens. Serial monitoring of inflammatory markers and markers of worsening right heart function may allow early detection and treatment of worsening PHN and/or sepsis.

Serial biomarkers such as B-type natriuretic peptide (BNP) have revealed prognostic value in PHN and serum levels decrease with functional improvement [14]. Measures of BNP levels provide a biomarker that differentiates infants with PHN physiology from those with pulmonary causes of respiratory failure and monitors worsening right heart function [11]. No BNP levels were obtained in this retrospective series, but as awareness of PHN grows, serial BNP levels should be part of a PHN care strategy in omphalocele infants.

The detection of delayed PHN should be aggressively managed as suggested by this series where only 50% survived despite treatment with nitric oxide, sildenafil and milrinone, escalating to ECMO in one case. One received the endothelin-receptor antagonist, Bosentan and sildenafil, for over one year and recovered. Since multiple mechanisms are involved in the pathogenesis of PHN, drug combinations with different sites of action should be considered in its management [15].
Follow-up echocardiograms revealed PHN resolved in the three survivors, which implies a reversible phenomenon. If successfully supported, an infant may survive. Whether the non-survivors developed irreversible physiology is unknown, but based on these infants, one should consider every option in the armamentarium for treating PHN when it appears later in the course of omphalocele infants.

References