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Joanne E. Baerg

Arul Thirumoorthi

Whitney Carlton

Shelly Haug

Andrew O. Hopper

See next page for additional authors

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Creator(s)

Joanne E. Baerg, Arul Thirumoorthi, Whitney Carlton, Shelly Haug, Andrew O. Hopper, Donna Goff, Sandhya Ramlogan, and Shawn D. St Peter

Late onset of pulmonary hypertension and sepsis in omphalocele infants

Joanne E. Baerg [a,*], Arul Thirumoorthi [a], Whitney Carlton [a], Shelly Haug [a], Andrew O. Hopper [a], Donna Goff [a], Sandhya Ramlogan [b], Shawn D. St. Peter [b]

[a] Loma Linda University Children's Hospital, 11175 Campus Street, Loma Linda, CA 92354, USA
[b] Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO 64108, USA

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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.

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An omphalocele is a ventral defect of the umbilical ring with herniation of the abdominal viscera [1]. For omphalocele infants, respiratory failure at birth is an independent predicator of mortality [2]. Pulmonary hypoplasia, defined as incomplete lung development, with decreased broncho-pulmonary segments and diminished alveolar septation, may contribute to respiratory insufficiency after birth in some, but not all, omphalocele infants [3]. Pulmonary hypertension (PHN), diagnosed between the second and seventh day after birth, is an independent predictor of mortality in omphalocele infants and may represent another cause of respiratory insufficiency [4,5].

A subset of omphalocele infants has no evidence of pulmonary hypoplasia or hypertension at birth, but exhibit respiratory insufficiency after the first week of life. These infants may have a late diagnosis of PHN. Although respiratory insufficiency is considered an important factor in omphalocele outcomes, little is known about this entity.

We report six infants with an omphalocele and a late diagnosis of pulmonary hypertension. On the basis of the findings of these cases and a literature review, strategies to promote recognition and treatment of this entity are discussed.

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 mm when observed in the setting of hypoxemia [6]. The omphalocele defect was

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 urosepsis, 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 occurred when she was septic.

The three that required conventional ventilation at birth, escalated to high frequency oscillatory ventilation (HFOV) (infants 4–6). When respiratory failure worsened in the sixth infant, a decision was made for veno-venous ECMO.

Infant outcomes are presented in Table 4. All three mortalities died within two months after birth at a median of 22 days (range: 18–51 days). All had severe PHN at the time of death and none responded to aggressive treatment for PHN and sepsis. None were stable for repair of the omphalocele defect. One suffered an omphalocele sac rupture and was debrided several days before his demise and one died on ECMO.

The sixth infant developed persistent tachycardia on DOL 13 and was intubated emergently on DOL 14. An endotracheal tube culture was positive for Group B streptococcus. Despite HFOV and an FiO2 of 100%, his respiratory failure worsened. An echocardiogram confirmed severe PHN. The infant was placed on veno-venous ECMO on DOL 15.

The decision for veno-venous ECMO was based on the fact that the infant had been extubated and ventilating well during the first week of life. Review of the literature revealed a paucity of data to guide the clinical management. It appeared the new-onset of PHN 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 arterial 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, and they are tolerating full enteral feeds. Two 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.

Gender	Gestational age (weeks)	Birth weight (g)	Weight/length z-score at birth	Inborn	Giant defect	Age at diagnosis by prenatal US (weeks)	Prenatal US report, omphalocele contents and heart evaluation
F	35	2644	0.53	No	No	16	Small bowel, hydronephrosis, two vessel cord, ASD
M	39	3775	0.55	Yes	Yes	18	Liver, small bowel, stomach, polyhydramnios, normal heart
F	39	2325	−0.28	No	No	20	Small bowel, small VSD
F	37	2448	−1.5	Yes	Yes	22	Liver, large and small bowel, hydronephrosis, oligohydramnios, Prominent Right atrium
M	35	2555	0.75	No	Yes	20	Liver, large and small bowel, small ASD
M	38	2299	0.53	No	Yes	12	Liver, small bowel, stomach, normal heart

Table 2
Infant cardiopulmonary status at birth and during the first week of life.

Apgar 1 min	Apgar 5 min	Intubated at birth	Fi02 at birth (%)[a]	Initial echo report	Blinded echo review	Echo: CHD	DOL[c] first feeding	Genetic syndrome
8	9	No	21	No PHN	Mild PHN	Dextrocardia Small ASD	3	Fryn syndrome
8	8	No	21	No PHN	No PHN	Normal	3	
8	9	No	21	No PHN	Mild PHN	Small VSD	6	Goltz syndrome with cleft lip
1	7	Yes	Conv vent 55	No PHN	Mild PHN	Normal	46 (NJ feed)	
3	8	Yes	Conv vent 40	No PHN	No PHN	Small ASD	2 (gavage)	
8	5	Yes	Conv vent 30 Ext[b] DOL 3—15	No PHN	Mild PHN	Small PFO	7 (gavage)	

[a] Infants 1—3 breathed room air at birth.
[b] Extubated.
[c] Infants 1—3 nippled feedings.

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 3
Cardiopulmonary, sepsis, ventilation and inotrope data at deterioration.

Intubated DOL	Fi02[a]	ECHO DOL	Blood gas: base excess	Culture result	WBC/CRP	Vent (days)	Inotropes (days)	Milrinone and other (days)
12[b]	40	18	−4	Urine Enterobacter	11/4	10	4	4
9	75	9	−5	Blood Methicillin resistant Staph	22 w bands/24	42	8	10
4	40	15	−3	Blood Coagulase negative Staph	19/20	6	4	Esmolol SVT[d] on DOL 15
Intubated at birth[c]	HFOV 60	13	−9	Trachea Staph aureus (pneumonia)	12/17	868 (trach DOL 71)	10	11
Intubated at birth	HFOV 65	52	−5	Blood Coagulase negative Staph	19/16	200 (trach DOL 52)	5	5
Intubated at birth	HFOV 100	15	−2	Trachea Group B Strep (pneumonia)	18/18.4	4 (V-V ECMO)	3	3

[a] Infants 1—3 placed on conventional ventilation.
[b] CT Angio on DOL 20.
[c] CT Angio and Cardiac Cath on DOL 117.
[d] Supraventricular tachycardia

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

Outcome DOL F/U	Last echo DOL	Medication respiratory status	Neurologic status at hospital d/c (MRI results)	Omphalocele Repairs DOL	Feeding status at F/U	Other operations DOL
Died 22 Sepsis	PHN 22	Fi02 100%		Not repaired	NPO	
Died 51 Sepsis	PHN 48	Fi02 100%		Not repaired	NPO	Sac rupture-debrided 46
Alive 1219	No PHN 30	No meds Room air	Frontal lobe atrophy	Primary and G-tube 38	Full G-tube feeds	SBO,[b] malrotation, perforation 45
Alive 868	No PHN 727	Sildenafil Fi02 25%	HIE[a] Motor and cognitive delay	Not repaired	Full NJ feeds	Left CDH[c] repair 800
Alive 540	No PHN 100	No meds Room air		Staged Final 151	Nippling full feeds	
Died 18 Sepsis	PHN 17	V-V ECMO		Not repaired	NPO	

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

considered predictive of increased postnatal morbidity in ompha-locele infants. These measurements represent incomplete lung development (pulmonary hypoplasia) which may contribute to respiratory insufficiency in some omphalocele infants, but is not a complete explanation. In this setting, a fixed respiratory insufficiency exists at birth.

In contrast, four infants in our series experienced little influence from pulmonary hypoplasia. They ventilated well on room air at birth, had satisfactory Apgar scores and nippled their first feedings, including one that subsequently required ECMO support.

A mortality rate as high as 25% is reported for omphalocele infants [1]. Pulmonary hypertension (PHN) is associated with mortality in omphalocele infants, independent of pulmonary hypoplasia or other causes, but few studies exist [4].

Pulmonary hypertension is an independent risk factor for mortality in infants with late-onset sepsis [8]. The mortality rate for infants with sepsis is between 7 and 12% and increases if PHN develops. Group B streptococcus sepsis also carries a high risk of complications from the development of PHN [9]. Three infants in this series with risk factors for mortality died. All had sepsis, PHN, one suffered a sac rupture and one was culture positive for Group B streptococcus.

The explanation for worsening PHN in omphalocele infants remains unknown. In some, isolated PHN in the absence of a CHD has been documented on prenatal echocardiogram [10]. The developing lung is subject to multiple genetic, pathological and environmental influences that can adversely affect development leading to PHN. New classifications of PHN may account for this diversity such as maladaptation, excessive muscularization and remodeling, and vascular hypoplasia as observed in CDH [11]. One infant responded well to long-term sildenafil and Bosentan, an endothelin receptor antagonist that improves pulmonary vascular resistance through remodeling. This favorable response implies a component of muscularization may contribute to PHN in omphalocele infants. Recent experience suggests Bosentan is well-tolerated and effective for pediatric PHN [12].

All six infants had culture proven evidence of sepsis, worsening acidosis, elevation of inflammatory markers and escalation of cardiopulmonary support. Echocardiograms performed at deterioration confirmed significant PHN. Although this is a small retrospective series, it reveals an important, previously unreported pattern, of worsening PHN with sepsis in omphalocele infants.

One infant died after three days of veno-venous ECMO support at eighteen 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.

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