Black lung persistent pulmonary hypertension of the newborn. *Saudi experience with sildenafil and nitric oxide*

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ABSTRACT

Objectives: To determine the clinical presentation, risk factors, diagnosis, and treatment outcome of Saudi infants with black lung persistent pulmonary hypertension of the newborn (PPHN).

Methods: This is a retrospective review of all neonates with PPHN presented to the Armed Force Hospital Southern Region, Kingdom of Saudi Arabia from January 2012 to December 2014.

Results: Ten term and near term infants presented with PPHN were included. Maternal diabetes and Down syndrome were the most common identified risk factors for PPHN in the study group. Nine infants were treated with oral sildenafil and did not require mechanical ventilation. Only one infant required mechanical ventilation and inhaled nitric oxide in addition to oral sildenafil.

Conclusion: Most of the patients in this cohort with PPHN had risk factors, they did not require mechanical ventilation and responded well to oral sildenafil.

Saudi Med J 2017; Vol. 38 (1): 97-100
doi: 10.15537/smj.2017.1.16223

During the intrauterine life, the foetus acquires oxygen by means of low resistance circulation of placenta and its pulmonary vascular resistance (PVR) is high as lungs get filled with fluid. During birth, when air enters the lungs and the umbilical cord gets clamped, the condition gets reversed with the decline in the PVR due to pulmonary vasodilatation with rising systemic vascular resistance (SVR), and oxygenation due to elimination of low resistance circuit of placenta.[1] In persistent pulmonary hypertension of the newborn (PPHN), such a transition is disturbed that results in sustain PVR increase. In this condition, PVR is known to exceed the SVR that results in right-left hemodynamics shunts through ductus arteriosus and patent foramen ovale leading to the vicious hypoxaemia cycle, causing pulmonary vasoconstriction leading to systemic hypoxaemia and decline in pulmonary perfusion.[1] Persistent pulmonary hypertension of the newborn is a major clinical problem in the neonatal intensive care unit (NICU), contributing to mortality ranging from 10% to 20% and morbidity ranging from 12% to 25% in full term and preterm infants.[2] The incidence of severe PPHN is estimated to be 2 per 1000 live born term infants.[2] The newborn suffering from PPHN is typically a term or near term infant having lung pathology including group B streptococcal (GBS) congenital pneumonia, meconium aspiration syndrome, and pulmonary hypoplasia as in congenital diaphragmatic hernia, in addition to hyaline membrane disease. It occurs within hours of birth with severe respiratory failure that requires intubation and mechanical ventilation.[1,3] Recent PPHN therapies comprise of alkalosis, sedation, relaxation, muscle paralysis, mechanical ventilation, as well as vasorelaxants. It is essential to take a close look at the drug regimen, indicating that medications are optimally dosed and appropriate.[4] Currently, inhaled nitric oxide (INO) is regarded as a gold standard therapy. However there are approximately 30% of the patients who are non-responsive to the treatment of INO.[1] Neonatal literature on idiopathic persistent pulmonary hypertension with normal lung (black lung PPHN) and its contribution to hypoxic respiratory failure in term and near term infant is scarce. Therefore, we opted to review our experience with black lung PPHN. In this case series, we delineate the clinical presentation, risk factors, and the challenge in diagnosis and management of infants with black lung idiopathic persistent pulmonary hypertension.

Methods.

This case series study was conducted at the Armed Force Hospital in the South region, Khamis Mushait city, located in the middle of Asir province in the Kingdom of Saudi Arabia. The city is at an altitude of 1850 m above the sea between longitudes 42-43 and latitudes 18-18.

This hospital is a 60-bedded, well-equipped tertiary referral hospital, which provides level 3 neonatal intensive care services. The hospital hosts 5,000-6,000 deliveries per year, and receives both normal and complicated deliveries, in addition to prenatally diagnosed malformations.

This data was collected over a 3-year period from January 2012 to December 2014. All admissions to

Disclosure. Author has no conflict of interests, and the work was not supported or funded by any drug company. The project was suppoted by the King Saud University through Vice Deanship of Research Chairs, Riyadh, Kingdom of Saudi Arabia (Grant no. 537821).

the neonatal intensive care unit during this period were reviewed. All infants with the diagnosis of PPHN were identified according to the documented diagnosis on the NICU records and included in this study. The findings consistent with PPHN include, presence of right ventricular hypertrophy (RVH), tricuspid regurgitation (TR) with jet pressure of >40 mm Hg and right-to-left or bidirectional hemodynamic shunting at the ductus arteriosus or at patent foramen oval. Further review of the respiratory, cardiac, and radiological manifestations was undertaken to identify infants with black PPHN. These are infants with PPHN who were admitted with severe hypoxemia without respiratory distress, and normal "well aerated lungs" demonstrated on chest x-rays. In total, 10 term and near term infants were included. Infants who were transferred from other hospital were excluded from this study. Also, infants who did not have echocardiography performed were excluded.

Table 1 - Antenatal and neonatal characteristics of the recruited infants with primary pulmonary hypertension of the newborn.

Variable	Number
Mean maternal age (year)	28 ± 2
Antenatal aspirin (No)	4/10
Mean gestational age (week)	37.6 ± 2.6
Cesarean/NVD	6/4
5 min Apgar score	8
Gender male/female	7/3
Birth weight (gram)	2460 ± 645
Age at presentation (hours)	3.6 (1-8)

NVD - normal vaginal delivery

Table 2 - Clinical presentation and diagnosis of infants with primary pulmonary hypertension of the newborn.

Presentation	Number
Hypoxia	10
Onset <24 hours	10
Oxygen saturation	76% ± 5
Metabolic acidosis	6/10
Mean potential hydrogen	7.19 ± 0.23
Respiratory distress	3/10
Loud second heart sound	6/10
RVH and tricuspid regurgitation	10
Mean pulmonary pressure	40 ± 5

RVH - right ventricular hypertrophy

Table 3 - Associated risk factors for primary pulmonary hypertension of the newborn.

Associate diagnosis	N (%)
Down syndrome	4/10 (40)
Severe hemolysis	1/10 (10)
Severe combined immune deficiency	1/10 (10)
Infant of diabetic mother	4/10 (40)

The data were analysed using the Statistical Package for the Social Science version 18 (SPSS Inc., Chicago, IL, USA). Mean, median, and standard deviations were used for descriptive data.

This study was approved by the Research Ethics Committee of the Armed Force Hospital Southern Region, Khamis Mushait, Kingdom of Saudi Arabia.

Results. Ten neonates satisfied the diagnosis of black PPHN with respiratory, cardiac, radiological, and echocardiographic evidence of PPHN and were admitted with severe hypoxemia without respiratory distress and normal "well aerated lungs" demonstrated on chest x-rays. **Table 1** shows the antenatal and neonatal characteristics of the study group.

Normal structure of the heart was observed in all newborns. The mean pulmonary pressure was 45 ± 5 mm Hg (**Table 2**). Right ventricular hypertrophy and tricuspid regurgitation (TR) were observed in all infants. The mean PH was 7.19 ± 0.23.

Table 3 shows the associated risk factors for black lung PPHN in our cohort. Four out of 10 infants of diabetic mothers and 4 out of 10 infants with Down syndrome (DS) were the most common associated risk factors. No antenatal exposure to medication, except aspirin, which was observed in 4 infants. In general, 9 out of 10 infants were treated with oral sildenafil for 10-14 days, and did not require mechanical ventilation. Three out of 10 were managed by oxygen through nasal CPAP, and 6 out of 10 were managed by nasal cannula. Only one infant with severe combined immune deficiency syndrome and black lung PPHN required intubation, mechanical ventilation, and INO in addition to oral sildenafil. This patient was ventilated for 20 days and discharged after 2 months on oral sildenafil.

Discussion. In this study we documented black lung PPHN in 10 term or near term infants who had respiratory, cardiac, and echocardiographic manifestations of PPHN. In addition, all these babies had severe hypoxemia without respiratory distress and with normal "well aerated lungs" demonstrated on chest x-rays. Therefore, these infants were labeled as black lung PPHN. Neonatal PPHN is rare and known to affect 1 or 2 infants per 1000 live births.[1,2] Typically, neonatologists face cases of PPHN secondary to underlying lung pathology with severe respiratory failure that requires intubation and mechanical ventilation. If left untreated, PPHN may lead to death. In this case series, we report persistent pulmonary hypertension of

the newborn in 10 infants who had normally aerated black lungs. All cases were term and near term with mean gestational age of 37.6 ± 2, which may rule out the risk of surfactant insufficiency, leading to PPHN in preterm infants.[4] Antenatal exposure to non-steroidal anti-inflammatory medication and serotonin reuptake inhibitor causing premature closure of PDA was reported as a cause of PPHN.[5]

In such a series, only 4 out of 10 mothers had received aspirin during pregnancy, but no evidence of premature duct closure was observed. Chambers et al[5] have demonstrated that non-steroidal anti-inflammatory drugs, such as ibuprofen and naproxen are frequently found in meconium of infants suffering from PPHN (even with a negative maternal history).[5]

Furthermore, concentration of the drugs in the meconium correlated with the incidence and severity of idiopathic PPHN. The meconium drug levels were not measured in this series due to the lack of this facility. All cases were presented with cyanosis and low oxygen saturation, along with 3 out of 10 mild or no respiratory distress, as well as mild metabolic acidosis in 6 out of 10 with a mean PH of 7.16, raising the possibility of right out flow obstruction groups of cyanotic congenital heart lesion. However, this possibility was excluded by echocardiographic findings in our patients.

Real-time echocardiography combined with Doppler flow studies remain to be gold standards for diagnosing PPHN demonstrating an increase in pulmonary pressure more than mean systemic blood pressure and right-to-left shunting across a patent foramen oval and a ductus arteriosus with Tricuspid insufficiency. Evan et al[6] reported a same range of results in term of neonates with hypoxic respiratory findings.

The other striking findings reported by Evan et al[6] indicated no correlation between pulmonary blood pressure level and the degree of hypoxemia. There was no significant relation observed during the mode of delivery, Apgar score, gender, and birth weight in this series. Unlike infants with idiopathic PPHN, all our patients had risk factors and underline diagnoses. Forty percent of our patients have DS. This agrees with the findings of the prospective study of a birth cohort of children with DS born between 2003 and 2006 in the Netherlands, which reported an incidence of 5.2% of PPHN in DS, that was significantly higher than the general population (p<0.001).[7] Similarly, another retrospective study[8] conducted in Columbus children hospital, Ohio State, concluded that DS has 10 times increase incidence of PPHN as compared with historical controls of pediatric population regardless of baseline demographics.[8] Similar to previous studies on PPHN in DS, we demonstrated that our patients with DS had translucent well aerated lungs. Four of our patients in this cohort were infants of diabetic mothers who had no other predisposing factors for PPHN, such as birth asphyxia or meconium aspiration. However, all these 4 neonates were male infants born by elective cesarean section, that had been reported by Hernandez-Diaz et al[9] as independent factors associated with an elevated risk of persistent pulmonary hypertension of the newborn.

Various other risk factors were known to influence susceptibility of the high-altitude city on post natal pulmonary vascular adaptation. It may lead to PPHN and defect in oxygenation. This effect had been documented in literature with some ethnic groups and in animal studies.[10,11] The prognosis of our patients was excellent, as 9 cases responded to oral sildenafil. This has also been proved in the previous literature to be a standard therapy for PPHN.[12,13] The dose ranged from 0.3-1 mg/kg/dose every 6-8 hours. Our patients weaned from oxygen supply over 10 to 14 days with no major side effects. Only one infant in our cohort required INO together with mechanical ventilation. Inhaled nitric oxide is considered as a standard of care for infants with severe PPHN. However, this intervention requires well equipped neonatal unit with well trained staff. This may not be widely available in a big country such as in the Kingdom of Saudi Arabia. The limitations of this study include its retrospective nature and the relative small number of infants included.

In conclusion, the main risk factors included down syndrome and infants of diabetic mothers, especially male infants born through cesarean section. This study offered an insight into the etiology and predisposing factors to black lung PPHN in Saudi patients. The prognosis of our cohort was excellent with the use of oral sildenafil. Therefore, this study provides further evidence that the use of sildenafil in infants with black lung PPHN is effective and may be tried especially when inhaled nitric oxide is not available.

Acknowledgment. *The author thanks the King Saud University through vice Deanship of Research Chairs, Riyadh, Kingdom of Saudi Arabia for supporting this study. The author also acknowledges the assistance of all doctors and fellows from the Neonatal Intensive Care Unit at the Armed Forces Hospital Southern Region, Kingdom of Saudi Arabia who participated in this research and made a significant contribution to the success of this study.*

Received 24th August 2016. Accepted 22nd September 2016.

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Clinical Practice Guidelines

Clinical Practice Guidelines must include a short abstract. There should be an Introduction section addressing the objective in producing the guideline, what the guideline is about and who will benefit from the guideline. It should describe the population, conditions, health care setting and clinical management/diagnostic test. Authors should adequately describe the methods used to collect and analyze evidence, recommendations and validation. If it is adapted, authors should include the source, how, and why it is adapted? The guidelines should include not more than 50 references, 2-4 illustrations/tables, and an algorithm.