INVITED COMMENTARY

Acute Pulmonary Hypertension of Early Infancy – Is Thiamine Deficiency the Only Cause?

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Acute pulmonary hypertension (aPH) is common in preterm and term infants soon after birth in both high-income countries (HIC, approximately 2/1000 live births [1]) and low- and middle-income countries (LMIC, 1.2 to 4.6 per 1000 live births in Asia [2] and 1-3 patients per month or 1-3% of admissions in most NICUs in India [3]. It is often secondary to parenchymal lung disease such as respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), pneumonia/sepsis or congenital diaphragmatic hernia (CDH). Infants with aPH have high morbidity and mortality during the neonatal period. Exacerbation of chronic pulmonary hypertension (PH) associated with conditions such as bronchopulmonary dysplasia (BPD) or CDH is common during early infancy. However, new onset aPH beyond the neonatal period during early infancy is uncommon in HIC.

In contrast, several case reports from the Indian subcontinent and case series describe aPH during early infancy in LMICs, especially among those exclusively breastfed by mothers on polished rice diet [4-8]. These cases presenting in the post-neonatal period are associated with lactic acidosis, hypoperfusion, often with severe pulmonary hypertension and hypoxemia [4]. Although, some of these infants have low thiamine levels and respond to pulmonary vasodilators and thiamine, the precise etiology of infantile aPH in the Indian subcontinent is not known.

Pulmonary vascular resistance (PVR) is high in fetal period and varies with gestational age (**Fig. 1**). During the canalicular phase of lung development, there is a paucity of pulmonary vessels resulting in high PVR. With advancing gestation, pulmonary vessels increase, decreasing PVR. Late in gestation, during the alveolar phase, pulmonary vessels become sensitive to oxygen and hypoxic pulmonary vasoconstriction increases PVR. At birth, when alveolar oxygen increases, PVR decreases and pulmonary blood flow increases, establishing lungs as the organ of gas exchange [9]. In some neonates, PVR does not decrease at birth resulting in persistent pulmonary hypertension of the newborn (PPHN).

High PVR observed in aPH of early infancy can potentially occur from two processes: *i*) chronic elevation in PVR from fetal period or birth followed by an exacerbation (acute-on-chronic PH – dotted line in **Fig. 1**), or *ii*) normal transition at birth and decrease in PVR followed by acute exacerbation (dashed line in the figure). The pathophysiology and phenotype of infantile aPH could be one of three mechanisms viz., *i*) normal pulmonary vascu-lature with acute arterial vasoconstriction, *ii*) left ventricular dysfunction with pulmonary venous hypertension, and *iii*) chronic remodeled pulmonary vasculature with superimposed arterial and venous hypertension. There is a desperate need for lung biopsy or autopsy data evaluating the morphology of pulmonary vasculature in these patients.

The exact etiology of aPH among Indian infants is not clear despite several publications; although, thiamine deficiency has been considered as a plausible explanation [5-7]. In this issue of *Indian Pediatrics,* Aroor, et al. [10] provide a large series of cases of aPH presenting in early infancy in a tertiary care institution. They provide data showing that the institution of a protocol of thiamine supplementation did not significantly alter mortality (28.6% without thiamine and 10.7% with thiamine, P=0.17). There are two major limitations to this study. No data on thiamine levels at the time of acute presentation are provided. It is possible that given the local diet that includes parboiled rice and fish, the prevalence of thiamine deficiency might be lower. Second, the sample size is small, increasing the risk of type II error. Hence, a clinically significant reduction in mortality, although not statistically significant, cannot be ignored. In addition, the authors [10] provide elegant data suggesting higher incidence of right and left ventricular dysfunction associated with higher mortality similar to that observed in infants with CDH and other causes of PPHN [10-13].

It is likely that cases of aPH in infancy are multifactorial in origin with nutritional (thiamine and other factors), infectious (viral, chlamydial, bacterial etc.) and genetic factors playing a role (**Fig. 1**). A large study that includes

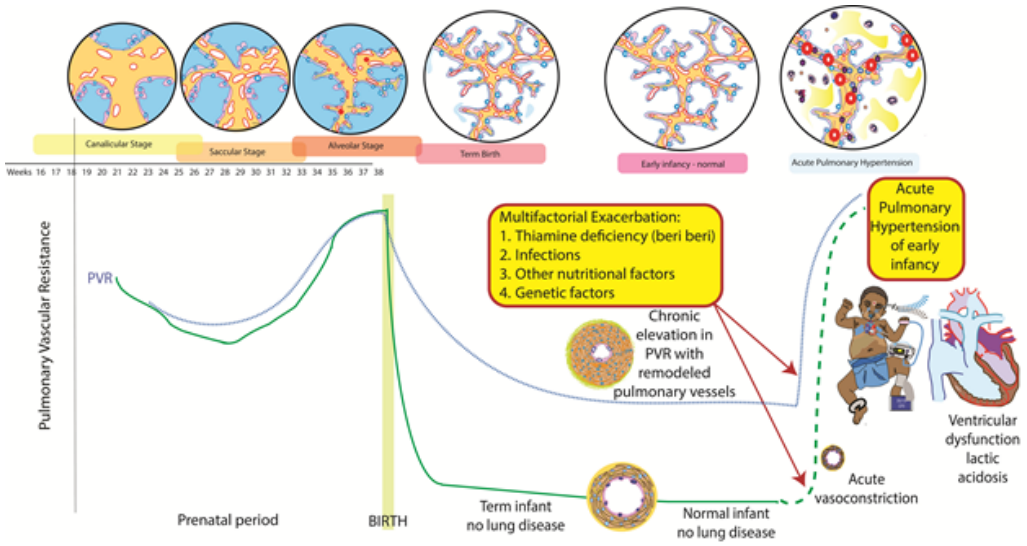

Fig. 1 Changes in pulmonary vascular resistance (PVR) during antenatal and postnatal periods. The solid line shows the variation in normal term infants. The dotted line shows the possible trajectory of PVR in chronic pulmonary hypertension with acute exacerbation. The dashed line depicts acute exacerbation in an infant with normal PVR prior to presentation.

estimation of thiamine levels in the mother and infant, lung biopsy or autopsy to evaluate pulmonary vascular morphology and if possible, a multi-center, randomized trial of thiamine infusion in aPH is warranted. Pending such studies, given the safety profile of thiamine, protocols that include supportive and pulmonary vasodilator therapy, and considering thiamine infusion (although the dose needs further evaluation) are justified in our opinion.

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REFERENCES

1. Walsh-Sukys MC, Tyson JE, Wright LL, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics. 2000;105: 14-20.
2. Nakwan N, Jain S, Kumar K, et al. An Asian multicenter retrospective study on persistent pulmonary hypertension of the newborn: incidence, etiology, diagnosis, treatment and outcome. J Mat Fetal Neonat Med. 2020;33:2032-7.
3. Singh P, Deshpande S, Nagpal R, Garegrat R, Gupta S, Suryawanshi P. Management of neonatal pulmonary hypertension-a survey of neonatal intensive care units in India. BMC Pediatr. 2023;23:149.
4. Panigrahy N, Chirla DK, Shetty R, et al. Thiamine-responsive acute pulmonary hypertension of early infancy (TRAPHEI)-a case series and clinical review. Children (Basel). 2020;7:199.
5. Sastry UMK, Kumar RK, Ghosh, S, et al. Thiamine-responsive acute severe pulmonary hypertension in exclusively breastfeeding infants: a prospective observational study. Arch Dis Child. 2021;106:241-6.
6. Sindhu TG, Rajesh TV, Ajithkumar VT, Muneer K. Thiamine-responsive acute pulmonary hypertension in an exclusively breastfed infant. Indian Pediatr. 2022;59:814-5.
7. Kundana PK, Reddy N, Reddy BS, et al. Thiamine-responsive, life-threatening, pulmonary hypertensive crisis with encephalopathy in young infants: A case series. Eur J Pediatr Neurol 2022;36:93-8.
8. Samprathi M, Mohammad F, Ramachandra P, Vemgal P. Case report: fulminant infantile beriberi: a report of six cases. Am J Trop Med Hyg. 2021;104:2238-40.
9. Lakshminrusimha S, Steinhorn RH. Pulmonary vascular biology during neonatal transition. Clinics in perinatology 1999, 26, 601-619.
10. Aroor S, Handattu K, Mundkur SC, et al. Severe pulmonary arterial hypertension in healthy young infants: single center experience. Indian Pediatr. 2023:S097475591600551. Epub ahead of print.
11. Patel N, Massolo AC, Paria A, et al. Early Postnatal ventricular dysfunction is associated with disease severity in patients with congenital diaphragmatic hernia. J Pediatr. 2018;203:400-7, e401.
12. Altit G, Bhombal S, Van Meurs K, Tacy TA. Ventricular performance is associated with need for extracorporeal membrane oxygenation in newborns with congenital diaphragmatic hernia. J Pediatr. 2017;191:28-34,e21.
13. Lawrence KM, Monos S, Adams S, et al. Inhaled nitric oxide is associated with improved oxygenation in a subpopulation of infants with congenital diaphragmatic hernia and pulmonary hypertension. J Pediatr. 2020;219:167-72.