NEONATAL HEMODYNAMICS Research Centre

Case Report

Detection of Pulmonary Hypertension in an Infant with Covid Related Chronic Lung Disease

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Key physiological insight/learning points:

Screening for pulmonary hypertension (PH) in infants with chronic lung disease should be strongly considered, regardless of etiology.

Echocardiographic parameters for PH assessment include estimated traditional assessment of severity (tricuspid regurgitation jet velocity and ventricular septal curve), but emerging measures like left ventricular end-systolic eccentricity index and PAAT/RVET ratio, as well as a comprehensive assessment of the RV function, may contribute to earlier detection of pulmonary vascular disease.

Neonatal SARS-COV2 infection may lead to severe chronic lung disease and subsequently result in chronic changes to pulmonary vasculature.

Background:

In infants with chronic lung disease, regardless of etiology, chronic pulmonary hypertension (PH) is a significant possible concomitant morbidity [1]. Although echocardiography is the most common screening tool used in the initial assessment of neonates at risk for PH [2] , the best parameters for early detection are yet to be established. Furthermore, there is a paucity of literature on the impacts of SARS-COV2 infection in neonates on long term pulmonary health. In this case, we present a late preterm infant diagnosed with peri-natal Covid-19, who went on to develop chronic lung disease and PH.

BW & Birth GA:

This is a case of a late preterm infant boy, born at $35^{2/7}$ weeks of estimated gestational age. Birth weight was 2520 grams.

Birth History:

Unremarkable pregnancy except for a Sars-CoV2 infection at 34 weeks (Delta variant). Mother was admitted for monitoring in the context of vaginal bleeding. The neonatal team attended the delivery: an urgent C-section for fetal decelerations. The baby was born non-reactive, without respiratory effort. Initial heart rate was below 60 bpm. Positive pressure ventilation was initiated following which the heart rate increased and the baby started breathing spontaneously. Apgar scores were 1 and 4 at one and five minutes, respectively. Cord PH was 6.9 with a base deficit of 18. The baby was admitted to our neonatal intensive care unit on continuous positive airway pressure.

Medical History:

On admission, the baby required intubation and mechanical ventilation due to significant respiratory distress. Neurological evaluation was compatible with moderate hypoxic ischemic encephalopathy and therapeutic hypothermia (TH) was initiated. The newborn was screened (as per our unit protocol) and found to be positive for Sars-CoV2 on the second day of life (DOL). TH was unremarkable and the infant was successfully extubated on DOL 4 and weaned to room air by DOL 6.

On DOL 10, the patient experienced acute respiratory deterioration. He required prolonged mechanical ventilation with high oxygen supplementation, respiratory physiotherapy, multiple and prolonged courses of post-natal steroids, prone ventilation, and sedation. Throughout the next five months, he had recurrent respiratory exacerbations, chronic severe cough (requiring gabapentin for

symptomatic control), severe gastro-esophageal reflux disease and respiratory support dependency (ongoing at 5 months of age). Chest radiography (Figure 1) and computed tomography (CT) (Figure 2) were compatible with fibrotic changes and significant diffuse lung injury. A comprehensive evaluation concluded the initial illness to be acute respiratory distress syndrome (ARDS) secondary to Covid with ongoing lung inflammation and developing chronic lung disease. Investigations included comprehensive genetic panels, infectious work-up (and exposure to antibiotic courses for possible bacterial concomitant respiratory infections), as well as involvement of numerous consultants (respiratory medicine, otorhinolaryngology, cardiology). A genetic panel for interstitial lung diseases, surfactant protein mutations and cystic fibrosis resulted negative. No infectious pathogens were found other than the initial SARS-COV-2.

Throughout the course of disease, multiple echocardiographic assessments were performed. Cardiac anatomy was normal, pulmonary veins were visualized on some of the evaluations without evidence of pathology, parameters regarding cardiac function and pulmonary pressure indices are summarized in Table 1. On DOL 101, the infant was found to have signs of underlying significant pulmonary vascular disease, and treatment with inhaled nitric oxide 20 ppm was initiated. Following that, he was bridged to Sildenafil.

Pulmonary imaging findings

Chest radiography and CT demonstrated multiple areas of ground glass opacities, volume loss, hyperinflation, atelectasis, with bronchiectasis and bronchial wall thickening.

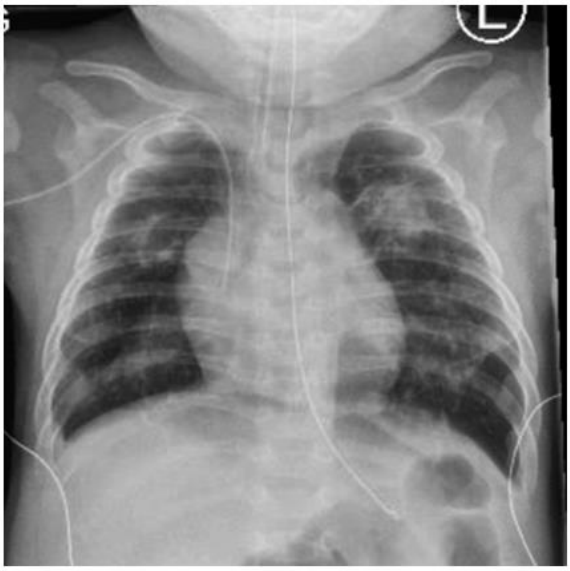

Figure 1: A demonstrative chest radiography.

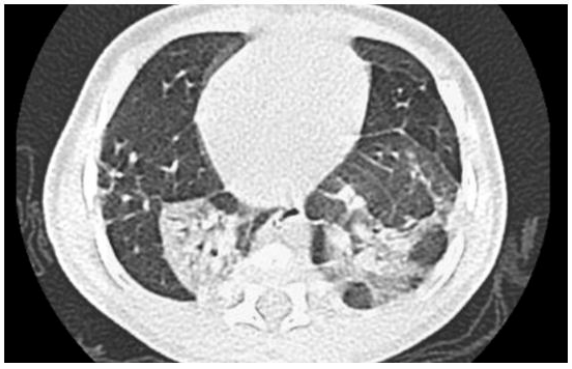

Figure 2: Lung CT axial view from mid-mediastinum level demonstrating bilateral disease with areas of bronchiectasis, atelectasis, and hyperinflation.

Hemodynamic consultation:

Significant PH requiring treatment (ventilation and comfort optimization, sildenafil) was recognized on DOL 101. Follow-up echocardiography demonstrated moderate improvement in most indices and the patient remained on sildenafil (see Table 1). Figure 3 depicts echocardiographic major findings. The patient had one event of pulmonary hypertension crisis with RV dilation requiring inhaled nitric oxide, milrinone and intravenous sildenafil in the weeks following PH diagnosis (DOL 150).

Outcome

Case still ongoing. The patient is about six months old and requires chronic respiratory support with pulmonary hypertension treatment, is fed through a gastric tube following fundoplication and suffers from complications associated with prolonged NICU hospitalization.

Discussion

Screening for PH is becoming standard of practice in preterm neonates with chronic lung disease[1, 3]. The most common screening method is echocardiography[1, 2], and the most common parameters used are the maximal estimated tricuspid regurgitation (TR) jet, and qualitative assessment of ventricular septal curve [1, 4]. Both parameters have limitations. In a survey of practice in north American NICUs, only a few sites reported using measures like end-systolic left ventricular eccentricity index (EI) (a quantifiable marker of septal deformation) and PAAT/RVET ratio (Pulmonary Artery Acceleration Time / Right Ventricular Ejection Time) routinely as indicators of high pulmonary vascular afterload[2]. Both markers have been shown to correlate with pulmonary pressure[5-7], however to our knowledge, no published studies compared the timing of diagnosis for each parameter. When examining the trajectory of parameters for our patient, these markers indicated earlier signs of pulmonary vascular disease. We suggest that it is prudent to follow infants more closely for significant PH when PAAT/RVET is <0.3 and EI is increasing. This may enable clinicians to recognize significant PH that requires treatment earlier.

Severe neonatal SARS-CoV2 infection is considered rare but has been described and studied increasingly over the past two years [8, 9]. Several case reports of preterm and near-term infants with severe ARDS were reported [10, 11], and prematurity was described as a risk factor for severe disease [12]. However, overall neonatal symptomatic infection rates are minimal, and most infants recover after a short duration of disease [9]. This case is, to our knowledge, a first description of a late preterm infant developing severe chronic lung disease following SARS-COV2 (Delta variant) infection. The chronic inflammatory process along with the need for prolonged respiratory support subsequently manifested in severe pulmonary hypertension in this infant.

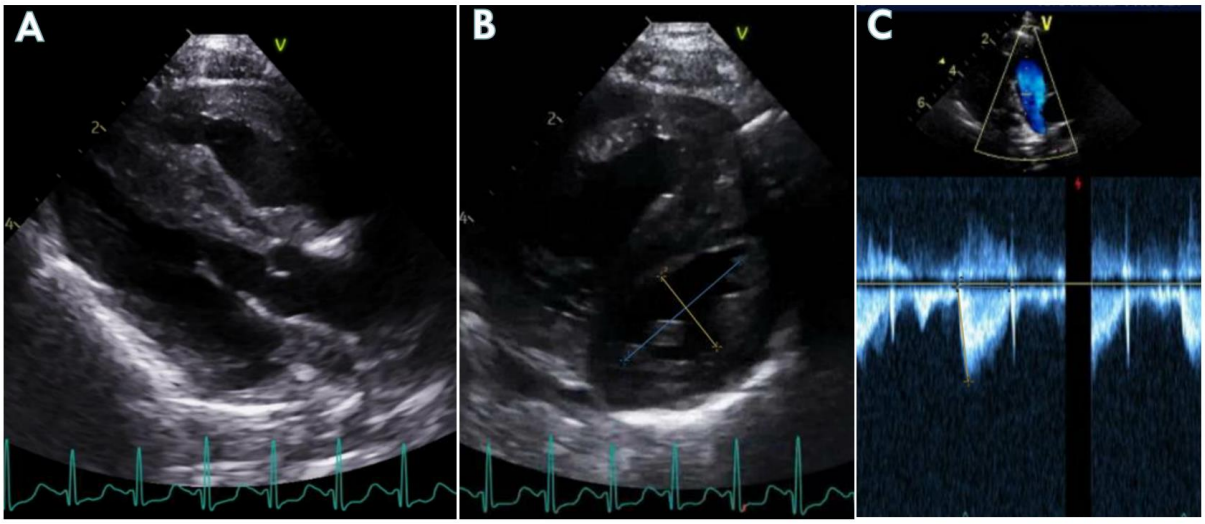

Figure 3: Echocardiography findings. A – Parasternal long axis showing the RV hypertrophy. B – Parasternal short axis view of the ventricles demonstrating septal flattening and an increased Eccentricity Index (>1.3). C – Pulse Wave Doppler of the RV outflow tract demonstrating a PAAT/RVET <0.3.

Parameter	DOL 15	DOL 25	DOL 55	DOL 67	DOL 101	DOL 108**	DOL 134**	DOL 150**
LV function*	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
RV function*	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Decreased
RV hypertrophy	None	None	None	None	RVH	RVH	Less RVH	RVH, fibrosis
TAPSE (mm)	-	-	7.2	-	9.1	-	11.5	8.6 (low)
RV/LV ratio	0.54	-	0.91	-	0.8	-	0.92	0.84
Septal curve	Round	Round	Round	Some flattening	Flat	Flat	Rounder	Flat
Max TR jet (sBP)	-	36 (73)	-	-	54 (79)	33 ()	37 ()	43 (93)
PFO shunt	-	Lt to Rt	Lt to Rt	Lt to Rt	Bidirectional	Bidirectional (Lt>)	Lt to Rt	Bidirectional (Lt>)
EI	0.8	-	1.05	1.32	1.61	1.46	1.26	1.39
PAAT/RVET	-	0.3	0.25	0.25	0.25	0.23	0.4	0.24
Corresponding Blood Gas PH/PCO2	7.29/53	7.34/46	7.36/51	7.32/59	7.26/79	7.29/64	7.29/56	7.44/43 (MV)

Table 1: Echocardiographic parameters over time. *Qualitative assessment. **Under PH treatment.
Abbreviations: EI – Eccentricity index, FAC – Fractional Area Change, LV – left ventricle, MV- Mechanical Ventilation, PAAT – Pulmonary Artery Acceleration Time, PH – Pulmonary Hypertension, PFO – Patent Foramen Ovale, RV – right ventricle, RVET – Right Ventricular Ejection Time, TAPSE – Tricuspid Annular Plane Systolic Excursion, TR – Tricuspid Regurgitation.

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