New-onset neonatal pulmonary hypertension associated with a rhinovirus infection

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A 3.5-week-old male neonate who developed an upper and lower respiratory tract rhinovirus infection that was temporally associated with the development of severe pulmonary hypertension is described. Rhinovirus has not previously been associated with pulmonary hypertension. This child developed severe pulmonary hypertension with right ventricular failure, requiring mechanical ventilation, nitric oxide inhalation and, eventually, extracorporeal membrane oxygenation.

Key Words: ECMO; Neonate; Pulmonary hypertension; Rhinovirus; Right ventricular failure

A 3.5-week-old male neonate had an uneventful intrauterine period, delivery and neonatal course. However, three days before admission, he developed a clear, watery nasal discharge and nasal congestion. One day before admission, he developed a tactile fever and increased work of breathing during feeding. On the day of admission, he was brought to the emergency department, where he experienced a brief episode of paleness and blue colouration immediately after feeding. There were no other signs or symptoms. He was awake and moving all four limbs. The mother denied any feeding difficulties, diarrhea or rash. The child was not taking any home medication or herbal remedies. His physical examination was unremarkable, except for persistent mild sinus tachycardia and tachypnea for which he was started on supplemental oxygen via nasal cannula. His admission complete blood count, complete metabolic panel and chest x-ray (CXR) were negative. His antenatal laboratory and newborn screening tests were negative. However, over the next 24 h, he became increasingly tachypneic and tachycardic, with increasing work of breathing, occasional wheezing and episodes of acute oxygen desaturation. His supplemental oxygen was increased to 40%. His serial daily CXRs developed small patchy perihilar infiltrates, but never any lobar or generalized parenchymal infiltrations. A two-dimensional echocardiogram (2 DE) at this time suggested the presence of suprasystemic pulmonary hypertension. He was started on oral sildenafil, inhaled nitric oxide (iNO) via high-flow, high-humidity nasal cannula. iNO was initially started at 10 ppm, but rapidly increased to 30 ppm, and his oxygen concentration was increased to 100% at a rate of 5 L/min because of increasingly frequent episodes of acute pulmonary hypertensive crises with acute desaturations and hypoperfusions. This occurred despite a nursing policy of minimal handling and agitation, and maintaining his oxygen saturation at >97%. At approximately 44 h postadmission, he was electively endotracheally intubated, mechanically ventilated, and sedated and paralyzed. His initial ventilatory settings were: pressure regulated volume (PRVC) control mode with a tidal volume of 9 mL/kg, a synchronous intermittent mandatory ventilation rate of 30 L/min, an inspiratory time of 0.6 s, a positive end-expiratory pressure of 5 cmH₂O, a fraction of inspired oxygen (FiO₂) of 70% and an iNO of 40 ppm. We were able to rapidly wean his FiO₂ to 55% and his peak inspiratory pressure (PIP) dropped from 25 cmH₂O to 20 cmH₂O. His capillary blood gases were pH 7.4, PO₂ 46 mmHg, PCO₂ 47 mmHg and HCO₃ 27 mmol/L. Attempts were made to keep the patient slightly

Une hypertension pulmonaire néonatale *de novo* associée à une infection par le rhinovirus

Les auteurs décrivent le cas d'un nouveau-né de 3,5 semaines de sexe masculin qui a contracté une infection des voies respiratoires supérieures et inférieures par le rhinovirus, laquelle était liée dans le temps à l'apparition d'une grave hypertension pulmonaire. Le rhinovirus n'a pas été associé à l'hypertension pulmonaire auparavant. Ce nourrisson a présenté une hypertension pulmonaire grave accompagnée d'une insuffisance ventriculaire droite exigeant une ventilation mécanique, l'inhalation d'oxyde nitrique, puis une oxygénation extracorporelle.

hyperventilated with a PCO₂ between 30 mmHg to 35 mmHg by increasing his ventilatory rate to 34 L/min; his FiO₂ was adjusted to maintain oxygen saturation at least >97%. He appeared to better tolerate the PRVC mode versus pressure control mode with less frequent episodes of pulmonary hypertensive crises. During these pulmonary hypertensive crises, he required additional sedation and hand bagging with 100% oxygen. At approximately 87 h post admission, he experienced a severe pulmonary hypertensive crisis that required the initiation of an intravenous dobutamine infusion, prolonged use of 100% oxygen, and increased iNO up to 60 ppm and hyperventilation with a tidal volume (TV) of 15 mL/kg resulting in a respiratory alkalosis and hyperoxia. His capillary blood gases were pH of 7.5, PCO₂ of 29 mmHg and PO₂ of 175 mmHg. A 2 DE confirmed worsening suprasystemic pulmonary hypertension. There was bowing of the interventricular septum toward the left ventricle with a moderately dilated and hypertrophic right ventricle (RV) compressing the left ventricle (LV). His brain natriuretic peptide (BNP) level was 590 pg/mL. A decision was made to transfer him to a quaternary intensive care unit (ICU) for possible extracorporeal membrane oxygenation (ECMO). For the next 8 h, while awaiting transfer, the patient improved such that his BNP level dropped to 458 pg/mL, and his ventilatory setting was weaned to pressure control mode with a PIP of 25 cmH₂O, positive end-expiratory pressure of 5 cmH₂O and an intermittent mandatory ventilation rate of 25 L/min with an FiO₂ of 85% and an iNO of 20 ppm. Throughout his stay, it was never difficult to maintain his PCO₂ within normal limits using ventilation. His PIP never rose above 25 cmH₂O. His oxygen saturation was more dependent on his degree of pulmonary hypertension and right to left shunting, than on his lungs' ability to transport oxygen from his alveoli to the blood.

In the quaternary ICU, he remained relatively 'stable' for the next 16 h at which time he experienced another severe pulmonary hypertensive crisis and was emergently put on venoarterial ECMO. After six days of venoarterial ECMO, he was transitioned to mechanical ventilation and iNO. His pulmonary hypertension, followed by serial echocardiograms and BNP levels, gradually improved over this period. Nineteen days after initial presentation, he was taken off iNO and extubated to high-flow nasal cannula humidified oxygen. Twenty-one days after initial presentation, his echocardiogram revealed a pulmonary pressure that was approximately 0.75 systemic with moderate RV dilation, severe RV hypertrophy, flattened interventricular septum

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and persistence of the mild tricuspid regurgitation and patent foramen ovale with bidirectional shunting. There was a new right atrial pericardial effusion. Qualitatively, the RV diastolic and systolic function remained markedly decreased; the LV systolic function was normal. Forty-five days after initial presentation, computed tomography angiography and cardiac catheterization revealed increased pulmonary resistance, but subsystemic pressures that were not responsive to NO or oxygen, normal pulmonary veins and possible ground-glass atelectasis. The overall picture was believed to suggest mixed lung disease and pulmonary hypertension. Seventy-three days after the initial presentation, an echocardiogram showed further improvement in the patient's pulmonary hypertension, with only mild to moderately diminished RV systolic shortening, mild to moderate dilation and hypertrophy of RV, and flattened ventricular septum in relation to LV. His BNP level had fallen to 161 pg/mL. Seventy-eight days after initial presentation, he was discharged home on oral sildenafil and 1 L/min oxygen via nasal cannula.

The following day, the patient was readmitted for overnight observation because of an accidental overdose of sildenafil. He was feeding well, and taking full oral bolus feeding. His physical examination was within normal limits, without any signs or symptoms of an upper respiratory infection.

The following laboratory findings were significant: his respiratory virus polymerase chain reaction (PCR) panel was positive for rhinovirus; it was negative for respiratory syncytial virus (RSV), influenza A and B, adeno, parainfluenza and meta-pneumo viruses (a study with a 99% sensitivity rate); all bacterial cultures were negative; his milk scan and barium swallow showed mild clinically insignificant gastroesophageal reflux up to the mid esophagus without any aspiration; testing for surfactant deficiency was negative; and brain magnetic resonance imaging results were within normal limits.

DISCUSSION

We believe that the rhinovirus infection was the cause of this child's new-onset pulmonary hypertension. If this child had persistent pulmonary hypertension of the newborn, he would have presented much earlier in life and most likely with a more difficult neonatal course. Instead, he was a healthy newborn who had gained 650 g since birth. He presented with a three-day history of upper respiratory tract infection symptoms and a medically witnessed transient episode of cyanosis, which in retrospect, could have been due to acute right to left shunting through his still patent foramen ovale or acute right heart decompensation due to suprasystemic pulmonary hypertension. His essentially normal initial physical examination, CXRs and laboratory findings, including negative bacterial cultures, are consistent with this hypothesis. His persistent tachypnea, tachycardia and elevated BNP level were clues to his worsening right heart failure due to severe pulmonary hypertension. This was confirmed on his 2DEs. His worsening clinical course and subsequent improvement also support the hypothesis that his condition was related to an acute illness. His acutely worsening pulmonary hypertension in the first week of presentation coincided with the rapid replication phase of a rhinovirus infection. The amelioration of his suprasystemic pulmonary hypertension to subsystemic levels at three weeks after initial presentation was also consistent with the natural history of rhinovirus infection. Rhinovirus becomes minimally detectable in respiratory tissues after three weeks of infection, although it still can be detectable up to five weeks after infection when the antibodies levels to rhinovirus rise to a peak (1). The only positive finding found after extensive investigation in our patient was the presence of rhinovirus in the PCR respiratory panel. We did not repeat his respiratory panel on his second admission because he did not exhibit any symptoms of a respiratory tract infection and because by 79 days after his initial infection, his rhinoviral PCR panel should have become negative.

Rhinovirus has been associated with up to 35% of 'common colds'. However, to the best of our knowledge, rhinovirus has not been associated with pulmonary hypertension. Some serotypes of rhinovirus have been shown to infect the lower respiratory tract (1). Fitzgerald et al (2) reported evidence of pulmonary hypertension in four of six mechanically ventilated infants with acute RSV bronchiolitis. Castelli et al (3) reported a nine-month-old infant who died on the fifth postoperative day after surgical correction for aortic coarctation, with clinical and autopsy evidence of acute bronchiolitis and severe pulmonary hypertension and immunohistochemistry and electron microscopy evidence of RSV in the pulmonary tissue (3). There was good repair at the site of aortic coarctation. The development of small patchy perihilar infiltrates and wheezing in our patient was consistent with the development of acute bronchiolitis. Other viruses have been associated with the development of pulmonary hypertension, notably congenital echovirus 11 (4). Severe pertussis has also been associated with neonatal pulmonary hypertension (5), but our patient did not demonstrate any of the characteristic whooping cough or lymphocytosis. Severe bronchopneumonia has also been associated with pulmonary hypertension (6), but our patient did not show any evidence of this on CXRs. Seki et al (7) reported the first association of severe gastroesophageal reflux and aspiration pneumonia with the development of pulmonary hypertension in a two-month-old boy with Down's syndrome (7). Our patient did not have clinically significant gastroesophageal reflux. In fact, on resuming full oral bolus feeding, his pulmonary hypertension had improved.

SUMMARY

We believe that our patient had developed an acute upper and lower respiratory tract rhinovirus infection that was temporally associated with the development of severe pulmonary hypertension. The time course of the amelioration of his pulmonary hypertension was also consistent with a prolonged rhinovirus infection. However, given the wide prevalence of rhinoviral infections, we should be cautious in ascribing a direct cause and effect relationship. We should, however, be aware of its possible association, and look for additional cases to be reported.

The institutional review board of St Peter's University Hospital approved this project (CPHSR study # 10:47) and provided exemption of informed consent.

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