© Pediatr Med Rodz 2022, 18 (2), p. 175–181
DOI: 10.15557/PiMR.2022.0026

Dominika Paw[1], Małgorzata Sokołowska[1], Ewa Głuszczak-Idziakowska[1], Marta Walentowska-Janowicz[2], Joanna Schreiber-Zamora[1], Bożena Kociszewska-Najman[1]

Received: 16.06.2021
Accepted: 17.03.2022
Published: 16.09.2022

Non-standard therapeutic methods for severe bronchopulmonary dysplasia in a premature newborn – case report

Niestandardowe metody terapeutyczne ciężkiej dysplazji oskrzelowo-płucnej u przedwcześnie urodzonego noworodka – opis przypadku

[1] Department of Neonatology and Rare Diseases, Medical University of Warsaw, Warsaw, Poland
[2] Department of Paediatric Radiology, Medical University of Warsaw, Warsaw, Poland
Correspondence: Małgorzata Sokołowska, Bolkowska 2D/39, 01-466 Warsaw, Poland, e-mail: malgorzata.sokolowska95@gmail.com

ORCID iDs
1. Dominika Paw https://orcid.org/0000-0002-5733-7822
2. Małgorzata Sokołowska https://orcid.org/0000-0002-4929-931X
3. Ewa Głuszczak-Idziakowska https://orcid.org/0000-0003-0561-6093
4. Joanna Schreiber-Zamora https://orcid.org/0000-0003-2348-0345
5. Bożena Kociszewska-Najman https://orcid.org/0000-0002-9498-9918

Abstract

Bronchopulmonary dysplasia is a lung disease that is the most common complication of prematurity and the most common chronic lung disease in neonates treated with mechanical ventilation and/or oxygen therapy. Children with bronchopulmonary dysplasia are at risk of cardiovascular complications, such as pulmonary arterial hypertension and left ventricular hypertrophy. The presented case concerns a premature infant born at 24 weeks gestation with severe bronchopulmonary dysplasia complicated by pulmonary arterial hypertension, interstitial emphysema and emphysema. The patient was subject to non-standard therapeutic procedures including L-citrulline, which may have a beneficial effect on the treatment of complications of severe bronchopulmonary dysplasia. Despite proper treatment, it is not always possible to avoid severe complications of bronchopulmonary dysplasia. Currently, available therapies are not always fully effective and it is necessary to continue searching and implementing new treatments to lower the risk of infant death and minimise long-term complications.

Keywords: bronchopulmonary dysplasia, pulmonary arterial hypertension, L-citrulline, sildenafil

Streszczenie

Dysplazja oskrzelowo-płucna to choroba płuc, która jest najczęstszym powikłaniem wcześniactwa i najczęstszą przewlekłą chorobą płuc u noworodków leczonych mechaniczną wentylacją i/lub tlenoterapią. Dzieci z dysplazją oskrzelowo-płucną narażone są na powikłania sercowo-naczyniowe, takie jak nadciśnienie płucne czy przerost lewej komory serca. Przedstawiony w niniejszym artykule przypadek dotyczy wcześniaka urodzonego w 24. tygodniu ciąży z ciężkim przebiegiem dysplazji oskrzelowo-płucnej, powikłanej nadciśnieniem płucnym, rozedmą śródmiąższową płuc i bullami rozedmowymi. Oprócz standardowych metod terapeutycznych wykorzystywanych w leczeniu tej jednostki chorobowej u opisywanego pacjenta zastosowano niestandardowe postępowanie terapeutyczne, włączając do leczenia L-cytrulinę, co może mieć korzystny wpływ na leczenie powikłań ciężkiego przebiegu dysplazji oskrzelowo-płucnej. Pomimo prawidłowej terapii uniknięcie ciężkich powikłań dysplazji oskrzelowo-płucnej nie zawsze jest możliwe. Obecnie dostępne metody terapeutyczne nie zawsze są w pełni skuteczne i istnieje konieczność dalszego poszukiwania i wdrażania nowych sposobów leczenia w celu obniżenia ryzyka zgonu u niemowląt z dysplazją oskrzelowo-płucną i zminimalizowania odległych skutków powikłań tej choroby.

Słowa kluczowe: dysplazja oskrzelowo-płucna, nadciśnienie płucne, L-cytrulina, sildenafil

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a lung disease that is the most common complication of prematurity and the most common chronic lung disease in neonates. Mechanical ventilation, trauma due to oxygen therapy, inflammation and intrauterine infection are important factors contributing to abnormal lung development in premature infants. Infants with BPD are at high risk of cardiovascular complications, such as pulmonary arterial hypertension (PAH), left ventricular hypertrophy, and hypertension[1]. Severe BPD is defined as a need for oxygen therapy of >28 days and at least 30% additional oxygen supply, and/or respiratory support continued beyond 36 weeks of postmenstrual age (PMA)[2].

Disrupted lung development seen in this form of BPD impairs not only the growth of the airways but also the development of vasculature, including the capillary system essential for gas exchange. Vascular deficiency can lead to elevated pulmonary vascular resistance and PAH. Epidemiological studies have shown that 25% of premature infants with BPD develop PAH. The severity of BPD positively correlates with the risk of PAH and, consequently, with increased mortality, as well as the duration and costs of hospital stay[3].

In addition to prematurity-related lung immaturity immediately after birth, resuscitation and the use of respiratory support may result in an injury in the infant that further restricts lung growth. Factors that can cause further lung damage include perinatal and secondary infections, atelectasis, barotrauma due to mechanical ventilation, and oxidative stress. Impaired development of the airway epithelium in BPD leads to vascular endothelial growth factor (VEGF) deficiency, which in turn disrupts the epithelial/endothelial-mesenchymal interaction[4].

The diagnosis and treatment of PAH in patients with BPD requires a multidisciplinary approach. ECG screening plays an important role not only in the diagnosis, but also in assessing treatment response, especially in children with severe BPD. After initial screening, cardiac catheterization remains the reference method and should precede pulmonary vasodilator therapy. However, due to the condition of patients with severe BPD and PAH, echocardiography may be more appropriate due to the need for continuous intensive medical therapy, as well as the risk of potential complications of general anaesthesia[3]. Echocardiographic evidence of PAH is found in 25–37% of infants with BPD[1,5].

Pulmonary vasodilators are increasingly used in the neonatal population, but there is very little data on long-term efficacy and safety of these drugs. Vasodilators other than inhaled nitric oxide mainly include sildenafil. However, it is believed that sildenafil should be used as an adjunct or secondary treatment to support lung protective strategies to reduce the risk of BPD, limit further lung injury, and promote normal lung development and growth in the vascular area. Such lung-protective strategies include limiting exposure to barotrauma and high oxygen levels in the breathing mixture, avoiding intubation with preferential use of non-invasive ventilation, and early extubation[2]. Current research points to new factors, including L-citrulline[6].

Pulmonary interstitial emphysema (PIE) is another complication associated with prematurity, respiratory distress syndrome and, most of all, mechanical ventilation. One lobe or both lungs may be involved. While conservative therapy is an acceptable form of initial treatment in most cases, unstable patients may require surgery[7].

BPD patients can develop pneumatocele, which are air-filled, thin-walled cysts that are formed in the lung interstitium as a result of air leakage and occur in 1.8% of premature infants under 30 weeks gestation[8]. The pathophysiology of these changes is debated but is believed to be due to acute pulmonary injury from mechanical ventilation-induced barotrauma. Additionally, oxygen and oxygen free radicals cause damage to the epithelial lining of the lung parenchyma, causing inflammation. When combined, these factors lead to check-valve-type airway obstruction, air entrapment and pseudocyst formation[8].

The purpose of this paper is to show that currently available therapies are not always fully effective in preventing severe complications of BPD. There is a need to continuously search for and implement new and effective treatments to reduce the risk of death in infants with severe BPD and minimise the long-term complications of this disease.

CASE REPORT

A first-pregnancy female neonate was born at 24 1/7 weeks gestation by caesarean section due to placental abruption. The pregnancy was complicated by the risk of premature birth. The mother received a complete course of prenatal steroid therapy completed 4 days before delivery with intramuscular betamethasone given in two doses of 12 mg every 24 hours. The child's birth weight was 680 g (42nd percentile according to the Fenton charts), body length 33 cm (Fenton 72nd percentile), and head circumference 22 cm (Fenton 37th percentile). The child had an Apgar score of 3/7/7 at 1/3/5 minutes after birth, respectively. The child was born without spontaneous breathing, flaccid, with heart rate of about 60/min. Five inflation breaths were applied, resulting in an increase in heart rate above 100/min. Breathing function appeared, but due to the weak respiratory drive and extreme immaturity of the child, the newborn was intubated and invasive mechanical ventilation was initiated at 5 minutes of life.

Respiratory problems

Increasing oxygen demand (up to 40% in the breathing mixture) and decreased lung transparency with

DOI: 10.15557/PiMR.2022.0026

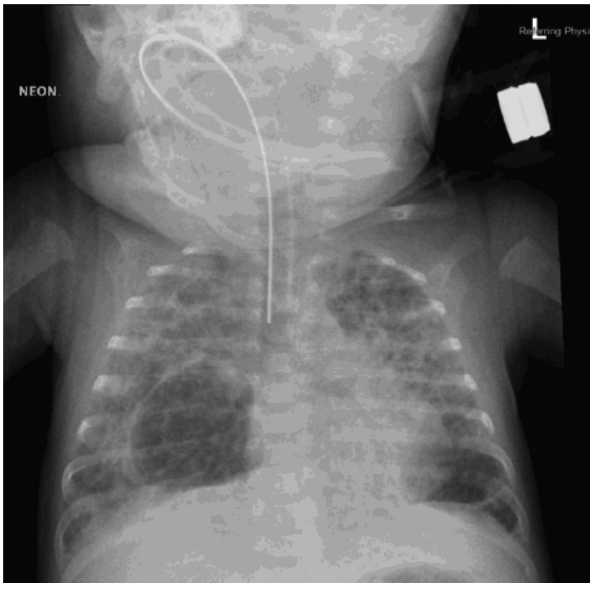

Fig. 1. Parenchymal/interstitial densities in both lungs, more intense on the right side. Features of interstitial emphysema. Among the densities on the right and left there are large circular radiolucent areas

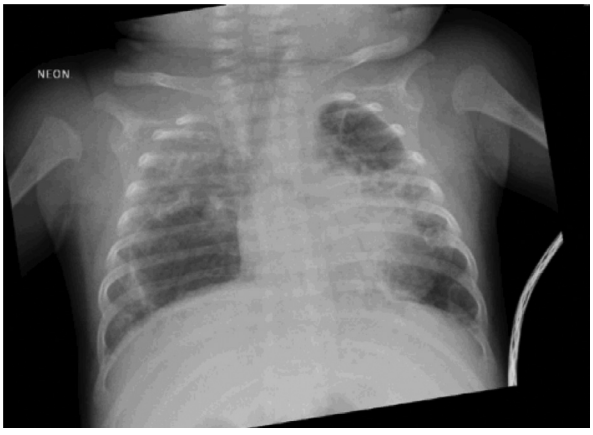

Fig. 2. Progression of atelectasis in the middle field of the left lung. Air-limited spaces in the lower fields of both lungs; massive interstitial changes in the right lung and smaller in the left lung, indicative of bronchopulmonary dysplasia

obliterated cardiac silhouette on chest X-ray were observed. Respiratory distress syndrome was diagnosed based on the clinical picture. On the first day of life, the infant received two doses of surfactant through the endotracheal tube (at 2 and 13 hours of life). The first dose was 200 mg/kg b.w., the second – 100 mg/kg b.w. On day 2 of life, there was massive bleeding from the respiratory tract. Changes indicative of PIE were seen on chest X-ray. On day 13, a 7-day intravenous betamethasone course was included, starting with 0.3 mg/kg b.w./day in 2 divided doses, with gradual dosage reduction. The girl was extubated on day 18. Non-invasive respiratory support (NIRS) was used. Due to the development of secondary generalised infection (of unknown aetiology) and ventilatory pneumonia, the child again required invasive mechanical ventilation after 2 days. From day 20 of life, emphysematous bullae were observed on chest X-ray (Figs. 1, 2). The child was consulted several times by a paediatric surgeon. Due to the general condition of the patient, a wait-and-see strategy was adopted. From day 20 of life, a second, 6-day course of steroid therapy with hydrocortisone at 5 mg/kg b.w./day (in 4 divided doses) was included, with gradual dosage reduction. No satisfactory effect was achieved. The newborn infant still required invasive conventional mechanical ventilation or high-frequency oscillatory ventilation until 64 days of life. The demand for oxygen fluctuated from 55% to 100% in this period. At 65 days of life, the child was extubated and NIRS was initiated with oxygen levels in the breathing mixture ranging from 40% to 30%. Computed tomography (CT) of the chest performed at 106 days of life confirmed massive architectural distortion with the presence of fibrous and cystic lesions nearly in the entire lungs. In the medial part of the right lung, at the level of the middle lobe, an approximately 3 cm air bulla was visible, causing pressure on the hilar structures with secondary vasodilation and distension of the middle lobe, in which no changes described in the course of BPD were visible. Two large subpleural bullae, 2.5 cm and 2 cm in size, were found in the left lung, at the level of segment 1/2 and segment 8/4–5 (Fig. 3 A–C). The girl required passive oxygen therapy from 137 days of life (43 5/7 weeks of post-conceptual age) until discharge.

Cardiac problems

The newborn infant repeatedly underwent echocardiography from birth. Heart defect was excluded. On day 2 of life, signs of PAH were found. On day 5 of life, a follow-up ECHO showed a narrow, patent ductus arteriosus with left-to-right shunt, but no signs of PAH. From day 9 of life, intraventricular constriction of the outflow tract from both ventricles was observed. From day 17 to day 41 of life, oral propranolol was included at 1 mg/kg b.w./dose every 8 hours due to persistent concentric hypertrophy of both ventricles (image as in cardiomyopathy with constricted outflow tract from both ventricles). On day 24, a decision was made to include a phosphodiesterase-5 inhibitor (sildenafil) at 1 mg/kg b.w./dose every 12 hours and a diuretic (spironolactone – 1 mg/kg b.w./dose every 12 hours). From 87 days of life, after obtaining the approval of the Bioethics Committee (at the Medical University of Warsaw, opinion number: KB/11/2021 dated February 19, 2021), L-citrulline at a dose of 150 mg/kg b.w./day was additionally included as a life-saving therapy. The child's respiratory and circulatory condition stabilised. Sildenafil and L-citrulline were continued until 162 and 157 days of life, respectively. The diuretic (spironolactone) was discontinued after 3 months due to severe osteopenia of prematurity.

 DOI: 10.15557/PiMR.2022.0026

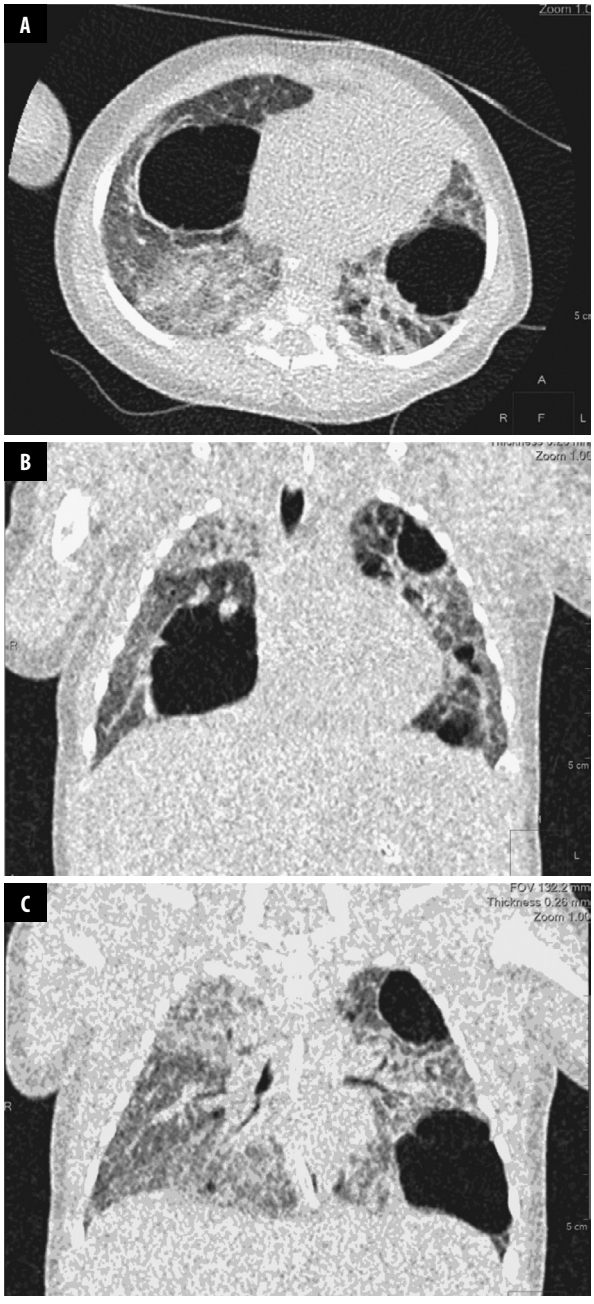

Fig. 3. A–C. Massive architectural distortions with the presence of fibrous and cystic lesions filling nearly the entire lungs. In the medial part of the right lung, at the level of the middle lobe, a large air bulla about 3 cm in size is visible. In the left lobe, two large subpleural bullae 2.5 cm and 2 cm in size, are seen at the level of segment 1/2 and segment 8/4–5

Infectious problems

After birth, laboratory findings indicated leukopenia of 2.92 × 10^3/μL (reference: 4–10 × 10^3/μL), rejuvenated white blood cells (the ratio of young white blood cells – WBCs to the total WBCs: 0.26; reference: <0.2), neutrophil vacuoles and thrombocytopenia (63 × 10^3/μL; reference: 150–400 × 10^3/μL). The identified congenital infection of unknown aetiology was initially treated with ampicillin at 50 mg/kg b.w./dose every 12 hours and gentamicin at 5 mg/kg b.w./dose every 48 hours. Due to the lack of response, ampicillin was discontinued on day 4 of life, and piperacillin with tazobactam at 100 mg/kg b.w./dose every 12 hours was added to gentamicin. On day 7 of life, *Staphylococcus capitis* was detected in blood cultures. Based on the obtained antibiogram, the antibiotic therapy was modified, vancomycin was included at 10 mg/kg b.w./dose every 12 hours. This treatment was continued for 10 days. On day 20, due to an increase in WBCs to 47.62 × 10^3/μL (reference: 4–10 × 10^3/μL) and normal C-reactive protein levels, nosocomial sepsis was diagnosed without pathogen isolation from blood cultures. The child received vancomycin at 10 mg/kg b.w./dose every 12 hours and meropenem at 20 mg/kg b.w./dose every 8 hours for 10 days. On day 33 of life, the girl was again diagnosed with ventilatory pneumonia based on chest X-ray and was put on ceftriaxone at 75 mg/kg b.w./dose every 24 hours for the next 13 days.

Nutritional problems

Immediately after birth, total parenteral nutrition was used, which was continued until 34 days of life. From day 9 of life, enteral nutrition was introduced (maternal breast milk/human milk from the Human Milk Bank), to which a human milk fortifier (BMF Bebilon – 3 sachets/kg b.w./day) was added on day 29 of life. Partial parenteral nutrition was continued from the day 34 to day 36 of life, and complete enteral nutrition was initiated on day 37 of life.

Calcium and phosphate metabolism problems

Periodic follow-up of calcium and phosphate metabolism revealed low serum levels of vitamin D_3 – 12.4 ng/mL (reference: deficiency 0–20 ng/mL; suboptimal/low 20–30 ng/mL; optimal 30–50 ng/mL; high 50–100 ng/mL; potentially toxic >100 ng/mL; toxic >200 ng/mL). Severe osteopenia of prematurity was diagnosed based on laboratory findings: phosphate reabsorption rate 78.13% (reference: 85–95%); calcium/creatinine ratio 0.05 mg/mg (reference: <0.8 mg/mg); phosphate/creatinine ratio 4.37 mg/mg (reference: 0.34–5.24 mg/mg) and osteopenic rib fractures on chest X-ray. The girl required BMF Bebilon human milk enhancer, a phosphate mixture and an increased supply of vitamin D_3 of up to 1,500 IU. The parameters of calcium and phosphate metabolism were normalised on discharge.

Haematological problems

During hospital stay, the child required multiple transfusions of leukocyte-poor blood components and irradiated red blood cells (15 mL/kg b.w./dose for 3 hours),

DOI: 10.15557/PiMR.2022.0026

leucocyte-poor platelet concentrates (10 mL/kg b.w./dose for 30 minutes) and fresh-frozen plasma (10 mL/kg b.w./dose for 30 minutes). At 3 months of life, supplementation with iron (5–9 mg/kg/day) and haematopoietic vitamins (folic acid – 1 × 2.5 mg/day and vitamin B_6 – 1 × 25 mg/day) was initiated. The use of erythropoietin to stimulate erythropoiesis was abandoned due to the development of severe retinopathy of prematurity (intravitreal ranibizumab was administered bilaterally on day 75 of life).

Neurological problems

Trans-fontanel ultrasonography (US) revealed a heterogeneous area in the right cerebellar hemisphere and features of bilateral lenticulostriate vasculopathy. The child was under the constant care of a physiotherapist, neurological speech therapist and neurologist. Neurological assessment showed slightly increased muscle tone in the upper and lower extremities. The child was undergoing continuous physical therapy. After discharge, the girl required further follow-up, tactile sensory stimulation, feeding training, correct positioning and kangaroo positioning.

***

At 7 months (55 0/7 weeks PMA, 15 0/7 weeks of corrected age), the girl was discharged from the hospital and placed under the care of a home hospice. The body weight on discharge was 4,680 g (Fenton 3rd–10th percentile), head circumference 37.5 cm (Fenton 3rd–10th percentile), and length 52.5 cm (Fenton 1st percentile). The child still required passive oxygen therapy with oxygen levels in the breathing mixture from 40% to 30%.

DISCUSSION

The incidence of severe BPD is inversely correlated with gestational age, estimated at 16% for all infants born at <32 weeks gestation and 40% for those born at ≤28 weeks gestation[9]. The pathophysiology of BPD is multifactorial. The immaturity of the lungs is combined with inflammation caused by infection, mechanical ventilation or chronic oxygen therapy, as in in the described case. There are various preventive approaches, ranging from ventilation to medical interventions. Prevention of BPD begins already in the prenatal period as both prenatal steroid therapy and surfactant treatment have been shown to reduce the incidence of respiratory distress syndrome and mortality. Neither of these interventions will protect against BPD, but the disease will be milder due to better postnatal health in newborns. At delivery, the management is focused on reducing exposure to intubation and invasive mechanical ventilation. The use of non-invasive respiratory support is preferred[2]. In the case of the described patient, it was not possible to avoid intubation and invasive mechanical ventilation immediately after birth despite a complete course of prenatal maternal steroid therapy. Also, the therapeutic administration of surfactant at 2 and 13 hours of life did not allow for early extubation. Invasive mechanical ventilation with high oxygen levels (fraction of inspired oxygen, FiO_2: 0.6–1.0) was necessary until 65 days of life.

The risk of BPD is increased by postnatal growth impairment. Proper nutritional treatment of children at highest risk of the disease is of key importance. In the presented case, complete parenteral nutrition was initiated immediately after birth. Despite covering the child's total caloric and fluid needs, postnatal growth retardation was observed, which may also have further aggravated BPD.

Treatment options for BPD are limited. Patient responses to therapies, including diuretics, inhaled corticosteroids, and inhaled beta2-agonists, vary considerably. Diuretics are commonly used to treat pulmonary oedema or fluid retention that may be related to BPD. However, they have not been shown to reduce the duration of respiratory support or the hospital stay. The use of diuretics poses a risk of electrolyte disturbances, including problems with calcium and phosphorus metabolism[2]. In the described case, disturbances in calcium and phosphate metabolism and osteopenic rib fractures consequently required discontinuation of diuretic therapy.

Pulmonary vascular dysmorphia and impaired angiogenesis in BPD increase the risk of PAH[2]. Unlike older children and adults, treatment options for children with BPD using conventional pulmonary vasodilators may be limited due to developmental pulmonary disease and a lower number of blood vessels for dilation[3]. The use of sildenafil, which acts by inhibiting phosphodiesterase-5, increasing the availability of cyclic guanosine monophosphate in vascular smooth muscle cells, leads to their dilatation and inhibition of vascular smooth muscle proliferation in patients with PAH[10,11]. During follow-up of infants with chronic pulmonary disease and PAH, it was found that long-term sildenafil therapy was associated with reduced echocardiographic features of PAH in the majority of patients (88%), with no significant adverse events[10].

Additionally, there is growing evidence that impaired L-citrulline–L-arginine–nitric oxide pathway is involved in the pathogenesis of chronic cardiovascular diseases, including chronic hypoxic PAH in neonates. L-citrulline prevents the reduction of the dimeric/monomeric endothelial nitric oxide synthase ratio in endothelial cells of pulmonary arteries, which is responsible for increased nitric oxide production. Preliminary research findings suggest that L-citrulline supplementation is a potential treatment for chronic PAH in infants with BPD[12]. Therapeutic strategies that increase the transport or levels of L-citrulline could provide a novel approach for the treatment of PAH in infants[5].

In the described case, L-citrulline was used as an additional, life-saving therapy.

 DOI: 10.15557/PiMR.2022.0026

Children treated with vasodilators for PAH should undergo echocardiographic evaluation prior to treatment discontinuation and in the case of pulmonary exacerbations. This tool assesses the velocity of the tricuspid regurgitation wave, the direction of leakage through a septal defect or patent ductus arteriosus, the degree of pulmonary regurgitation, and the nature of the pulmonary flow waveform[13]. Some cases of PAH may be overlooked if ECHO alone is performed, but it remains the best non-invasive screening tool for assessing PAH in neonates with BPD[9]. In the described case, follow-up echocardiography was performed systematically every 1–2 weeks, depending on the degree of respiratory failure in the patient. Cardiac catheterization was abandoned due to patient's respiratory and circulatory instability and the need for aggressive mechanical ventilation.

The brain natriuretic peptide (BNP) and its N-terminal cleavage product known as the N-terminal pro-brain natriuretic peptide (NT-proBNP), secreted by cardiomyocytes in response to ventricular wall tension due to pressure and/or volume overload, are good biomarkers of long-term treatment outcomes in PAH patients. In neonates, the absolute values of NT-proBNP show high interindividual variability, are strongly dependent on gestational and postnatal age, and are therefore of limited value in the diagnosis or determining the severity of PAH. However, the assessment of changes in NT-proBNP levels over time, when combined with echocardiography, is very useful for monitoring disease progression and/or response to treatment[13]. Unfortunately, in the case of the presented patient, NT-proBNP levels were not monitored.

BPD is additionally complicated by emphysema in 1.8% of premature infants born before 30 weeks of gestation, which was also found in the described newborn. Surgical intervention was repeatedly considered, but the condition of the child's respiratory system ruled out such a possibility. Bulla drainage and pleural drainage were considered only as life-saving procedures and only if conservative treatment failed. The risk of damaging the lung cysts or healthy lung parenchyma when inserting a chest tube is high. Ventilation may be significantly impaired in young newborns with cystic pulmonary tissue. Instead, a drain is inserted into the chest cavity in the event of tension pneumothorax or pneumothorax to evacuate air and improve pulmonary haemodynamics. Surgical intervention is considered to be reserved for non-responders and lesions limited to a single lobe[8].

Effective prevention of early BPD complications and their treatment gives a chance to minimise the long-term effects of the disease. A diagnosis of BPD is associated with poorer neurodevelopmental outcomes in premature infants. These children are at increased risk of cerebral palsy, delayed speech development, behavioural problems, attention disorders or cognitive delay causing learning difficulties[2]. Such patients require advanced, multidisciplinary medical care after discharge. The care plan should include elements of nutritional support, respiratory rehabilitation, developmental screening, and infection prevention, but should still be tailored to the individual patient's needs[2,13].

CONCLUSIONS

Children with extremely severe, ventilator-dependent BPD are more likely to experience serious complications, including PAH, growth disorders, and neurodevelopmental problems. Understanding the effects of antenatal, early postnatal, genetic or epigenetic factors, and comorbidities on the development of BPD is critical for improving late treatment outcomes in this group of children.

The coexistence of PAH, which reduces the child's chances for survival, is an important prognostic factor. New therapies with sildenafil and L-citrulline may improve the prognosis and increase therapeutic efficacy in PAH coexisting with BPD. However, further multicentre, randomised clinical trials are needed to confirm the safety and efficacy of this therapeutic approach.

The group of patients with BPD is very diverse, which is often associated with an unpredictable response to the treatment. It should be emphasised that severe forms of BPD will occur despite appropriate preventive measures, and the current lack of diagnostic guidelines and protocols, as well as effective treatment methods contributes to a significant diversification of treatment approaches in neonatal intensive care units, not only in Poland.

Conflict of interest

The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.

References

1. Kim DH, Kim HS, Choi CW et al.: Risk factors for pulmonary artery hypertension in preterm infants with moderate or severe bronchopulmonary dysplasia. Neonatology 2012; 101: 40–46.
2. Tracy MK, Berkelhamer SK: Bronchopulmonary dysplasia and pulmonary outcomes of prematurity. Pediatr Ann 2019; 48: e148–e153.
3. Christ LA, Sucre JM, Frank DB: Lung disease and pulmonary hypertension in the premature infant. Prog Pediatr Cardiol 2019; 54: 101135.
4. Yun EJ, Lorizio W, Seedorf G et al.: VEGF and endothelium-derived retinoic acid regulate lung vascular and alveolar development. Am J Physiol Lung Cell Mol Physiol 2016; 310: L287–L298.
5. Fike CD, Summar M, Aschner JL: L-citrulline provides a novel strategy for treating chronic pulmonary hypertension in newborn infants. Acta Paediatr 2014; 103: 1019–1026.
6. Lakshminrusimha S, Mathew B, Leach CL: Pharmacologic strategies in neonatal pulmonary hypertension other than nitric oxide. Semin Perinatol 2016; 40: 160–173.

7. Matta R, Matta J, Hage P et al.: Diffuse persistent interstitial pulmonary emphysema treated by lobectomy. Ann Thorac Surg 2011; 92: e73–e75.
8. Sacks GD, Chung K, Jamil K et al.: Surgical salvage of acquired lung lesions in extremely premature infants. Pediatr Surg Int 2014; 30: 573–576.
9. Abman SH, Collaco JM, Shepherd EG et al.; Bronchopulmonary Dysplasia Collaborative: Interdisciplinary care of children with severe bronchopulmonary dysplasia. J Pediatr 2017; 181: 12–28.e1.
10. Mourani PM, Sontag MK, Ivy DD et al.: Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. J Pediatr 2009; 154: 379–384, 384.e1–2.
11. van der Graaf M, Rojer LA, Helbing W et al.: EXPRESS: sildenafil for bronchopulmonary dysplasia and pulmonary hypertension: a meta-analysis. Pulm Circ 2019; 9: 2045894019837875.
12. Lauterbach R, Pawlik D, Lauterbach JP: L-citrulline supplementation in the treatment of pulmonary hypertension associated with bronchopulmonary dysplasia in preterm infant: a case report. SAGE Open Med Case Rep 2018; 6: 2050313X18778730.
13. Hansmann G, Sallmon H, Roehr CC et al.; European Pediatric Pulmonary Vascular Disease Network (EPPVDN): Pulmonary hypertension in bronchopulmonary dysplasia. Pediatr Res 2021; 89: 446–455.

 DOI: 10.15557/PiMR.2022.0026