CASE PRESENTATION

Pulmonary Hypertension in Children - New Insights of Diagnosis and Management

Ina PALII[1,2], Iulia RODOMAN[1,2], Daniela PALEGA[2], Lucia PIRTU[1,2], Svetlana SCIUCA[1,2,3]

Abstract

Pulmonary hypertension (PH) is a pathophysiological condition that includes multiple clinical situations and can complicate most cardiovascular and respiratory diseases[1]. Step by step diagnosis and reviewing contemporary treatment approaches would significantly impact the prognosis of pediatric patients with PH. Management of children with PH requires a multidisciplinary team with experience. PH is frequently associated with cardiac and pulmonary diseases with chronic hypoxia, obstructive respiratory disorders, chest malformations, pneumonia, acute respiratory distress, and can also develop during late phases of cystic fibrosis, bronchial asthma, bronchiectasis. Updated definition of PH at the world symposium (HTAP, Nice, 2018) includes values of pulmonary artery pressure >20 mmHg and using pulmonary vascular resistance (PVR) indexed to the body surface to identify pre-capillary PH, PVR≥3 WU×m^2 [5]. Cardiac catheterization represents the gold standard in diagnosing PH, being the most precise method of measuring the blood pressure (BP) in the pulmonary artery and offering valuable information about cardiac output, arterial pressure, and the response to pulmonary vasodilators[2,3]. The specific modern treatment with endothelin receptor inhibitors significantly improves the disease's clinical course and brings better parameters at instrumental investigations[8].

Keywords: pulmonary hypertension, endothelin receptors, pulmonary vascular resistance, cardiac catheterization, target therapy.

Rezumat

Hipertensiunea pulmonară (HTP) este o condiție fiziopatologică ce include multiple situații clinice și care poate complica majoritatea bolilor cardiovasculare și ale aparatului respirator[1]. Etapizarea diagnosticului și revizuirea schemelor terapeutice contemporane ar avea un impact semnificativ asupra prognosticului pacienților pediatrici. Managementul copiilor cu HTP necesită o echipă multidisciplinară cu experiență în domeniu. Foarte frecvent HTP este asociată anomaliilor de dezvoltare a cordului, dar și bolilor respiratorii caracterizate prin hipoxie cronică, tulburări obstructive, malformații ale cutiei toracice, pneumonie, detresă respiratorie acută. Definiția actualizată a HTP din cadrul celui de-al VI-lea simpozion mondial cuprinde presiunea în artera pulmonară >20 mmHg la nivelul mării și include utilizarea rezistenței vasculare pulmonare (RVP), indexată la suprafața corporală pentru identificarea hipertensiunii pre-capilare, definită de RVP≥3 WU × m^2 [5]. Cateterizarea cardiacă reprezintă standardul de aur în diagnosticul HTP, fiind cea mai precisă metodă de măsurare a presiunii sanguine în artera pulmonară. De asemenea, oferă informații valoroase despre debitul cardiac, presiunea arterială, răspunsul la tratamentul cu vasodilatatoare pulmonare[2,3]. Tratamentul specific modern cu inhibitori ai receptorilor de entodelină demonstrează o îmbunătățire semnificativă a stării clinice dar și a datelor investigațiilor instrumentale[8].

Cuvinte cheie: hipertensiune pulmonară, receptorii entodelinei, rezistența vasculară pulmonară, cateterizare cardiacă, terapie țintită.

CASE REPORT

A 6-years-old boy is admitted to the cardiology department with complaints of high fatigue, weakness, excessive sweating, and dry caught. Clinical examination revealed growth and development retardation (16 kg (25P), 105 cm (25P), 14.5 kg/m^2). The pale skin, periorbital circles, peripheral cyanosis with finger clubbing, and poorly subcutaneous adipose tissue are observed. No edemas were remarked. BP 90/55 mm/Hg measured on the right hand, SpO_2 - 96% at arms

[1] Department of Cardiology, PMHI Institute of Mother and Child, Chisinau, Republic of Moldova
[2] Department of Pediatrics, „Nicolae Testemitanu" University of Medicine and Pharmacy, Chisinau, Republic of Moldova
[3] Department of Pneumology, PMHI „Institute of Mother and Child", Chisinau, Republic of Moldova

Contact address:
Ina PALII, PMHI Institute of Mother and Child, Department of Pediatrics/Cardiology, 93vBurebista Street, Chisinau, Republic of Moldova.
E-mail: ina.palii@usmf.md

and 85% at feet, respiratory rate - 26/min. The limits of relative and absolute cardiac dullness are enlarged. On auscultation: moderate tachycardia with pronounced pulmonic component of the second heart sound and pulmonary valve regurgitation murmur.

The patient is born from the second pregnancy, accompanied by multiple acute viral respiratory infections, chronic fetal and placental insufficiency, chronic intrauterine hypoxia, and born prematurely at 29 weeks with a weight of 2100 grams and a height of 47 cm. After birth, echocardiography shows the presence of patent arterial duct (PAD). The alimentation is exclusively artificial. There is an insufficient weight addition in the first year of life, the child weight being just 8100 grams. The child is immunized according to the national vaccination plan. There is no history of cardiac diseases in the family.

Several chronological events can describe the patient's clinical condition. In 2019, at the age of 4, the boy started attending kindergarten, where he is inactive, prefers to stay alone, and does not participate in activities and games with other children. There are no abnormalities at echocardiography and no data for pulmonary hypertension or cardiac malformations. In 2020, at the age of 5, a dry cough appeared, and after a while, there is evident perioral cyanosis during physical effort, the child is tired, inert and also there is dyspnea which makes him refuse to play. At echocardiography, there is a right atrium walls hypertrophy (5mm), right atrium dilatation (16 mm), thickening of the mitral valve with insufficiency of I-II grades, severe pulmonary hypertension – 75-80 mmHg (Figure 1).

Further investigations are recommended at this stage. Later, in February 2020, the patient is investigated by CT Angiography (CTA) and is diagnosed with congenital cardiac malformation - PAD (7 mm in length and 9×7 mm in diameter) with high flow, the aortic and pulmonary connections of the PAD are not obstructive, the pulmonary artery trunk is extremely dilated (19×18 mm), right pulmonary artery dilatation 10 mm, left pulmonary artery 9mm, dilatation of right atrium and ventricle with severe pulmonary hypertension (Figure 2). In March 2020, the child is hospitalized in the surgical department with clinical signs of pulmonary hypertension, where a cardiac catheterization is performed and confirms the diagnosis of pulmonary hypertension. In order to estimate the possibility of surgical intervention on cardiac malformation, in March 2020, during another cardiac catheterization, multiple measurements are made with trying of PAD closing (Table 1).

According to existing data (Pulmonary Vascular Resistance 1.590 dynes*sec/cm5, Systemic Vascular Resistance 1.545 dynes*sec/cm5, PVR/SVR res ratio 1.03) the surgery is questionable, and pharmacological treatment is recommended starting with Sildenafil. In July 2020, the patient is investigated by echocardiography, and the pulmonary hypertension is still persistent 70 mmHg. The ECG (December 2020) reveals a sinus rhythm, heart rate 93/min, arrhythmia, right atrium and right ventricle hypertrophy. There are no specific important laboratory findings in the blood stream. In the same period, the patient is included in a rare disease program in the Republic of Moldova PH and starts his combined treatment with Bosentan and Sildenafil. The patient is frequently investigated to monitor his clinical stage and the response to treatment, measuring clinical parameters and comparing their values in time (Table 2).

DISCUSSIONS

Pulmonary arterial hypertension (PAH) is a disabling progressive disease characterized by an increase of pulmonary vascular resistance (PVR) caused by the

Tabel 1. The parameters of cardiac catheterization

Parameters of cardiac catheterization	Values
RV Max dP/dt [mmHg/sec]	938
RV Max dP/dt/P [l/sec]	22
HB [G/100 ml]	9.56
Cardiac Output [l/min]	11:25 3.52
Cardiac Index [l/min/m2]	5.75
Venous Site	PA
Heart Site	AO
Heart rate	98.00
Stroke Volume [ml/beat]	35.97
SVi [ml/beat/m2]	58.73
O2 consumption [ml/min]	118.3
Predicted Pulm Vasc Resist [dynes*sec/cm5]	1.73
Predicted Syst Vasc Resist [dynes*sec/cm5]	27.42
Pulm Vasc Resistance [dynes*sec/cm5]	1.590,.91
PVR IX [(dynes*sec/cm5)*m2)]	974.44
Total Pulm Resistance [dynes*sec/cm5]	1.670.45
TPR IX [(dynes*sec/cm5)*m2)]	1.023.12
Syst Vascular Resistance [dynes*sec/cm5]	1.545.45
SVR IX [(dynes*sec/cm5)*m2)]	946.60
TSR [dynes*sec/cm5]	1.727.27
TSR IX [(dynes*sec/cm5)*m2)]	1.057.96
PVR/SVR res ratio	1.03
TPR/TSR res ratio	0.97

Tabel 2. The dinamics of the efficiency criteria for Bosentan and Sildenafil treatment

Parameters	Before Therapy	After 1 month	After 3 months	After 4 months
Heart rate beat/min	93	99	72	75
Blood pressure mm/Hg	90/60	91/55	90/60	90/60
Saturation O_2 % hand/leg	97/68	99/70	96/76	97/80
6MWT (six minutes walk test) steps	420	427	485	500
MeanPAP	70	45	40-42	43
RVSP	70	45	42	43
CI	3.55	2.3	3.06	2.64

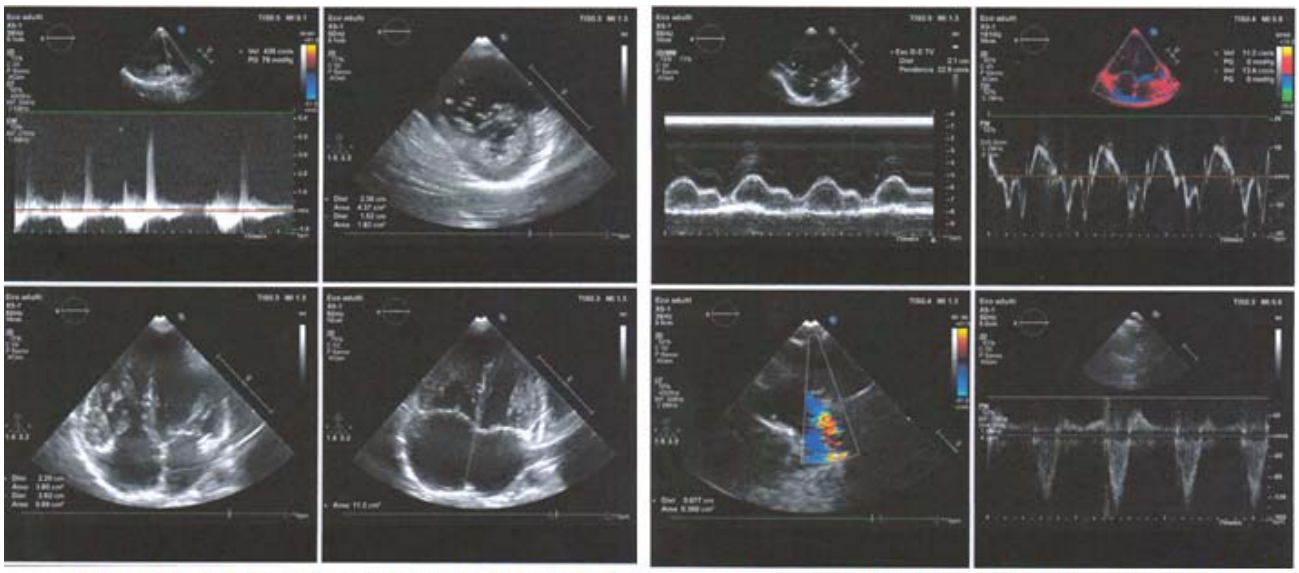

Figure 1. *Echocardiography. Tubular PAD 5-6 mm with laminar shunt right-left in systole and left-right in diastole. Aortic cross laminar flux. Significant right ventricle hypertrophy. TAPSE 1.6cm, without regurgitation in tricuspid valve. IAS, IVS without changes. Dilated inferior vena cava.*

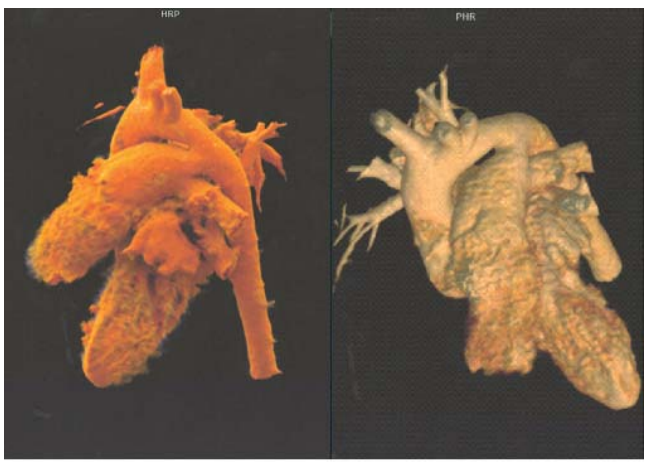

Figure 2. *CT angiography. Persistent arterial duct with large dimensions: length 7mm, diameter 9×7mm. Pulmonary artery dilatation, right atrium and right ventricle dilatation.*

vascular structural remodeling of pulmonary arteries, and frequently results in right ventricular failure 6. Cardiac catheterization has long served as the „gold standard" for the anatomic and physiological assessment of patients with CHD (Congenital Heart Diseases). The direct measurement of pressures within cardiac compartments and major vessels helps to classify patients according to risk, evaluate pharmaceutical involvement and indicate a need for intervention. Cardiac catheterization and angiography have significantly facilitated the diagnosis and the care of children with CHD and have increased the safety of surgery for CHD. There is an unwritten general rule that a contrast-enhanced computed tomography (CT) scan to be undertaken before cardiac catheterization, as it will allow a precise approach to cardiac catheterization,

and limit the radiopaque contrast required. CT scanning is beneficial to determine pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, or interstitial lung disease, the denial or evaluation of congenital lung or heart malformations (e.g., anomalous systemic or pulmonary drainage, pulmonary sequestration, aortopulmonary collaterals, lung hypoplasia, pulmonary vein stenosis, airway malformations), and the degree of parenchymal lung disease in bronchopulmonary dysplasia (BPD). There is a broad consensus that a diagnostic cardiac catheterization with acute vasoreactivity testing be undertaken at least once in any patient with significant pulmonary hypertension, mainly if specific pulmonary hypertensive therapy is recommended. In general, it is welcomed to repeat cardiac catheterization 6–12 months after initiating targeted PHVD therapy[3,7]. Endothelin-1 (ET-1) represents the key mediator in the pathogenesis of IPAH, with high concentrations in the plasma. Bosentan, an endothelin receptor antagonist, has been approved in Food and Drug Administration (FDA) to effectively improve IPAH when administered in recent studies[8].

In pediatric IPAH (Idiopathic pulmonary arterial hypertension), plasma endothelin levels are elevated, and ECE activity is enhanced. As a result, ET-1 is highly expressed in the lung. The overproduction of ET or over activation of ET-A receptors and low levels of ET-B receptors will come up with intense vasoconstriction of vessels and stimulate matrix production and cell proliferation, which resulting in fibrosis and inflammation of PAH. Furthermore, the levels of ET-1 are closely related to the levels of PVR. In this way, endothelin receptor antagonists are important in the treatment of IPAH. In *European Medicines Agency* (EMA), *Food and Drug Administration* (FDA), and *China Food and Drug Administration* (CFDA) emphasize that bosentan is recommended for the treatment of PAH to improve effort tolerance and symptoms in patients with WHO functional class III. The effectiveness has been demonstrated in primary PAH (idiopathic and familial), PAH secondary to scleroderma without significant interstitial pulmonary disease, congenital systemic-to-pulmonary shunts, and Eisenmenger syndrome[4].

Maybe in our clinical case there is a genetic predisposition for earlier development and rapid progression of the disease, so further genetic investigation are needed.

CONCLUSIONS

The presented clinical case demonstrates the severe and progressive course of pulmonary hypertension, which causes rapid invalidation and a considerable decrease in life quality. On the other hand, modern pharmacological approaches with specific therapy (endothelin receptor antagonist -Bosentan) reveal new perspectives of an effective treatment in similar cases and considerably improve the prognosis. All that is mentioned calls for responsibility and high professionalism regarding pulmonary hypertension since specific therapy initiated promptly represents the main source of life expectancy.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5) and the national law. Informed consent was obtained from the patient described in the clinical case and his parents.

References

1. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015; 46:903.
2. T. F. Feltes et al., "Indications for cardiac catheterization and intervention in pediatric cardiac disease: A scientific statement from the American Heart Association," Circulation, vol. 123, no. 22, pp. 2607–2652, 2011, doi: 10.1161/CIR.0b013e31821b1f10.
3. M. J. del Cerro et al., "Cardiac catheterization in children with pulmonary hypertensive vascular disease: Consensus statement from the Pulmonary Vascular Research Institute, Pediatric and Congenital Heart Disease Task Forces," Pulm. Circ., vol. 6, no. 1, pp. 118–125, 2016, doi: 10.1086/685102.
4. Y. Wang, S. Chen, and J. Du, "Bosentan for Treatment of Pediatric Idiopathic Pulmonary Arterial Hypertension: State-of-the-Art," Front. Pediatr., vol. 7, no. July, pp. 1–10, 2019, doi: 10.3389/fped.2019.00302.
5. Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019; 53.
6. R. L. E. van Loon et al., "Outcome of Pediatric Patients With Pulmonary Arterial Hypertension in the Era of New Medical Therapies," Am. J. Cardiol., vol. 106, no. 1, pp. 117–124, 2010, doi: 10.1016/j.amjcard.2010.02.023.
7. Miklashevich I.M., Shkolnikova M.A., Gorbachevsky S.V., Shmalts A.A., Groznova O.S., Sadykova D.I., Yakovleva L.V., Degtyarev D.N., Burov A.A., Ovsyannikov D.Yu., Volkov A.V. CONTEMPORARY STRATEGY OF PULMONARY HYPERTENSION MANAGEMENT IN PEDIATRICS. Cardiovascular Therapy and Prevention. 2018;17(2):101-124. (In Russ.) https://doi.org/10.15829/1728-8800-2018-2-101-124
8. Avitabile, C.M., Vorhies, E.E. & Ivy, D.D. Drug Treatment of Pulmonary Hypertension in Children. Pediatr Drugs 22, 123–147 (2020).