PEDIATRIC ALLERGY, IMMUNOLOGY, AND PULMONOLOGY
Volume 34, Number 1, 2021
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DOI: 10.1089/ped.2020.1244

Hepatopulmonary Syndrome and Multiple Arteriovenous Fistulas in a Child with Niemann-Pick Disease

Zeynep Reyhan Onay, MD,[1] Tugba Ramasli Gursoy, MD,[1] Ayse Tana Aslan, MD,[1] Tugba Sismanlar Eyuboglu, MD,[1] and Koray Akkan, MD[2]

Background: Niemann-Pick disease (NPD) is caused by abnormal storage of sphingomyelin. NPD may affect the pulmonary system and cause hypoxia. In the present case, both hepatopulmonary syndrome (HPS) and pulmonary arteriovenous fistulas (PAVFs) developed in a child with NPD and were successfully treated with repeated embolization.
Case Presentation: We have reported the case of a 16-year-old-girl with NPD who suffered severe hypoxia, dyspnea, fatigue, had multiple PAVFs, and was diagnosed with type 2 HPS. To improve oxygenation, 10 PAVFs were embolized. She needed re-embolization after 9 months because of hypoxia redevelopment.
Conclusions: Pulmonary involvement, HPS, and/or PAVFs could be responsible for hypoxemia in patients with NPD, who should, therefore, be investigated for HPS and PAVFs. Embolization could be beneficial. Some patients may need repeated embolization.

Keywords: embolization, hypoxia, Niemann-Pick disease

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Introduction

Niemann-Pick Disease (NPD) is an autosomal recessive disease caused by abnormal storage of sphingomyelin in the body. Among other systems, it can affect the respiratory system and cause restrictive lung disease. Clinical findings include cough, dyspnea, recurrent pneumonia, and hypoxia.[1,2]

Hepatopulmonary syndrome (HPS) is characterized by pulmonary vascular dilatation and causes reduced arterial oxygenation in patients with chronic liver disease. The body's response to hypoxia relies on nitric oxide as a mediator of intrapulmonary vascular dilatation. Mixed venous blood is rapidly transferred to the pulmonary veins to increase blood flow and maintain alveolar ventilation. This, however, can cause ventilation–perfusion mismatch. Clubbing, dyspnea, cyanosis, and hypoxemia may occur.[3]

Pulmonary arteriovenous fistulas (PAVFs) are rare abnormal vascular communications between pulmonary arteries and veins. In patients with chronic liver disease, the lungs contain dilated pre- and postcapillary vessels that bypass the liver due to portosystemic shunts secondary to liver failure, resulting in substantial diffusion defects. Another explanation could be that PAVFs develop secondarily to a blood flow distribution difference, with more flow to the lung bases than the apices, which might spread to all lung segments over time.[4]

Herein, we report the case of a 16-year-old girl with NPD and severe hypoxia. She had multiple PAVFs and was diagnosed with pulmonary involvement of NPD and type 2 HPS. Her oxygenation improved with embolization performed twice in the course of 9 months.

Case Presentation

A 16-year-old girl was diagnosed with NPD type B when she was 2 years old. Upon admission to our hospital, her oxygen saturation was 84% on room air, and her respiratory and heart rates were 26 and 90 per minute, respectively. She was suffering from fatigue and was unable to speak. On physical examination, growth retardation, severe digital clubbing, crepitant rale in the left lower lung, bronchial respiratory sounds in the right lower lung, splenomegaly (20 cm), and hepatomegaly (2 cm) were detected. She could not perform a pulmonary function test (PFT) due to muscle weakness. In a complete blood count, moderate thrombocytopenia ($67 \times 10E3/uL$) was detected, while the hemoglobin level was 14.3 g/dL and the white blood cell count was $4.19 \times 10E3/uL$. Regarding coagulation parameters, a prolonged activated partial thromboplastin time of 50 s, prothrombin time of 26 s, and an international normalized ratio of 2.45 were detected. Liver and kidney function tests were normal, and in the arterial blood gas analysis, pH was 7.41, pCO_2 was 38.5 mmHg, pO_2 was 53.8 mmHg, HCO_3 was 24 mmol/L, and SO_2 was 86.8%.

Thorax computed tomography angiography (CTA) revealed multiple PAVFs in the medial segment of the right

Departments of [1]Pediatric Pulmonology and [2]Interventional Radiology, Faculty of Medicine, Gazi University, Ankara, Turkey.

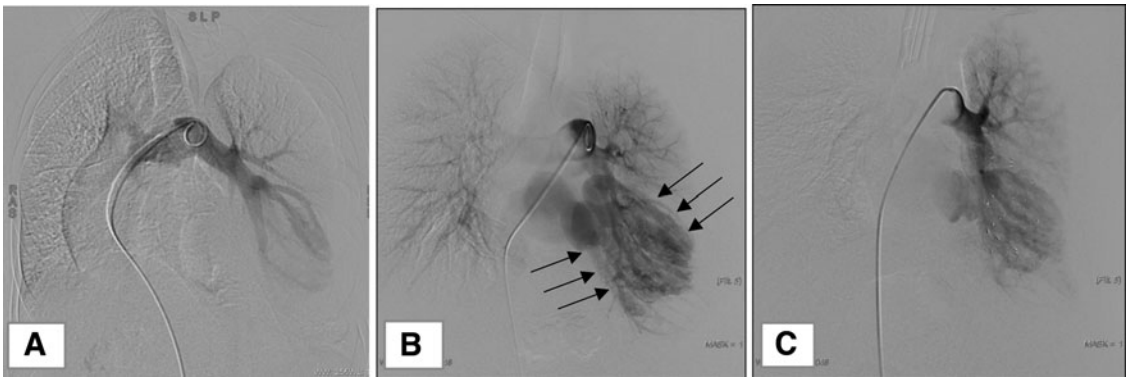


FIG. 1. **(A, B)** Pulmonary angiography images of arteriovenous fistulas including multifeeder high-flow varicose dilatation with a direct fistulous relationship and early feeding to the left heart through the pulmonary veins. **(C)** Pulmonary angiography image of multifeeder pulmonary arteriovenous fistulas embolized with 10 vascular plugs on the left lung.

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middle lobe and the laterobasal segment of the left lower lobe, which were related to pulmonary arteries. In addition, interlobular septal thickening in both lungs (mostly in the left lower lobe), ground glass opacities in the basal segment of the left lung and lingular segment were detected and these findings were evaluated as pulmonary involvement of NPD. She was diagnosed with type 2 HPS on the basis of multiple PAVFs on CTA, confirmed by angiography, and intrapulmonary shunting detected by saline contrast-enhanced echocardiography. The fistulas in the left lung were considered the main cause of hypoxia. Ten PAVFs were embolized with 5–12-mm vascular plugs (Amplatzer; St. Jude Medical, Inc., St. Paul, MN; Fig. 1). Owing to prolonged coagulation parameters, she was administered 1 U of fresh frozen plasma twice daily before and during embolization.

After embolization, the patient's oxygen supplementation requirement gradually decreased. Oxygen supplementation was terminated 6 days postoperatively. Her oxygen saturation was 96% on room air and her weakness diminished. She was able to speak and walk without support.

In the follow-up, she was admitted to the emergency department with cyanosis and dyspnea 9 months after embolization. Her oxygen saturation was 84% on room air. CTA was performed again. In the inferior zone of the left lung multifeeder, high-flow varicose dilatation with residual filling from the previous embolization and early drainage with pulmonary veins to the left heart were detected. Four of the 10 previously embolized fistulas were re-embolized with vascular plugs (Fig. 2). Parenchymal perfusion was nearly normal except in the paracardiac focal intense opacification area; therefore, embolization was not performed in the right lung. She showed rapid clinical improvement and hypoxia disappeared 1 day after re-embolization. She was now able to perform a PFT, which revealed a restrictive pattern [forced expiratory volume 1 (FEV_1): 42%, forced vital capacity (FVC): 43%, FEV_1/FVC: 105; and forced expiratory flow at 25–75: 45%]. A 6-minute 450-meter walk test was normal in the second month after reembolization. She had no hypoxia and was able to speak and walk comfortably for 7 months after the second embolization.

Written consents were obtained from both the patient and her parents.

Discussion

Severe hypoxia, due to a coexistence of pulmonary involvement of NPD, HPS, and PAVFs, was present in this patient, who was successfully treated with embolization. Reembolization was needed during her follow-up. Significant clinical improvement and an increase in the patient's ability to perform daily physical activities were observed. This condition is very rare and may be life threatening.

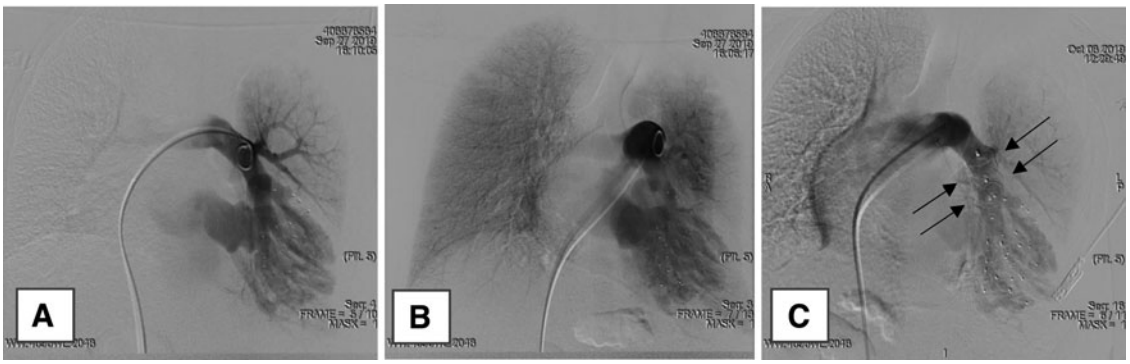


FIG. 2. **(A)** Pulmonary angiography image of preoperative early perfusional filling on the left lung and vascular plug view from previous embolization, **(B)** nearly normal parenchymal perfusion except focal intense opacification in the right paracardiac area and residual early perfusion filling in previously embolized areas on bilateral pulmonary angiography, and **(C)** 4 vascular plugs placed in the pulmonary arterial branch with residual filling in the left main pulmonary arterial catheterization.

Therapies with nitric oxide inhibitors, intravenous methylene blue (a guanylate cyclase inhibitor), sympathomimetic agents, somatostatin, almitrine, indomethacin, and plasma exchange have been tried in some studies to counteract vasodilatation and improve areas with low ventilation. Although they have shown some oxygenation improvement, no specific effective medical treatment for HPS exists, yet.[5] Surgery is a treatment option for PAVFs; however, it could not be performed on our patient due to prolonged coagulation parameters and multiple PAVFs in the lungs. Embolization was preferable in this case. It should be kept in mind, however, that re-embolization may be needed after some time.

Treatments for HPS aim to improve gas exchange, thus increasing the capacity for exercise and improving the quality of life.[5] The most effective treatment is liver transplantation. However, because our patient had type 2 HPS, it was contraindicated in this case. The patient underwent repeated embolization procedures to improve oxygenation. She did not have hypoxemia during the interim period.

In conclusion, patients with NPD should be examined for pulmonary involvement, HPS, and PAVFs. In cases wherein liver transplantation and surgical treatment of PAVFs are contraindicated, to improve patients' ability to perform daily physical activities, embolization should be considered. The possibility of hypoxia recurrence and a need for re-embolization should be kept in mind in the follow-up.

Informed Consent

Informed consent was obtained from both the patient and parents.

Consent for Publication

Consent for publication was obtained from both the patient and her parents.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

No funding was received for this article.

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Address correspondence to:
Ayse Tana Aslan, MD
Department of Pediatric Pulmonology
Faculty of Medicine
Gazi University
Besevler
Ankara 06500
Turkey

E-mail: aysetugbapp@gmail.com

Received for publication July 24, 2020; accepted after revision November 18, 2020.

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