Treatment of Congenital Generalized Lymphangiectasia With Propranolol in a Preterm Infant

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KEY WORDS
generalized lymphangiectasia, propranolol, VEGF, preterm infant

ABBREVIATIONS
VEGF—vascular endothelial growth factor
VEGFR-3—vascular endothelial growth factor receptor 3

Dr Poralla was responsible for medical care of the patient and drafted the initial manuscript; Dr Specht carried out the analyses of the lymphangiogenic factors; Dr Born interpreted MRI images and chest radiographs; Dr Annette Müller performed and interpreted histopathologic and immunohistochemical analyses; Dr Bartmann was responsible for the medical care of the patient and determined the therapy; Dr Andreas Müller was responsible for the medical care of the patient, determined the therapy, and coordinated assessment of the lymphangiogenic factors; and all authors reviewed and revised the manuscript and approved the final manuscript as submitted.

doi:10.1542/peds.2012-2087

Accepted for publication Jul 11, 2013

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275)

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
Generalized lymphangiectasia is a rare congenital disorder characterized by dilatation of lymphatic vessels, without an increase in their number or complexity, involving most frequently the mediastinum, lung, intestine, liver, spleen, and subcutaneous soft tissue. The disease can be difficult to differentiate from generalized lymphangiomatosis, because the histopathologic and radiographic findings are similar. Distinguishing features of generalized lymphangiomatosis include proliferation of complex anastomosing lymphatic channels with secondary dilatation, presentation most often in late childhood, and frequent involvement of extrapulmonary tissues, with lytic bone lesions and mediastinal soft tissue edema commonly observed. Generalized lymphangiectasia predominantly affects infants and is usually fatal, especially in children with thoracic lesions. The most common reported therapies include surgery, α-interferon, radiotherapy, and glucocorticoids.1,2

PATIENT PRESENTATION

In April 2011, a girl with hydrops fetalis and pathologic cardiotocogram was born at 32 2/7 weeks of gestation by cesarean delivery. Apart from the hydrops fetalis, which required pigtail pleuroamniotic shunts, pregnancy was uneventful. Family history was unremarkable.

Postnatally, the patient received mechanical ventilation and extensive therapy with catecholamines and diuretics. Pleural effusions and ascites were chylous (pleural effusion: triglyceride level, 227 mg/dL; 81% lymphocytes; ascites: triglyceride level, 459 mg/dL; 87% lymphocytes) and required drainage. Apart from massive generalized edema, clinical examination revealed dilated and dense lymphatic vessels in the axillae and groin.

Two attempts to extubate the infant failed within a few hours, most likely due to persisting generalized edema and presumably an increasing dilatation of the lymphatic vessels after termination of mechanical ventilation with high peak inspiratory pressure. MRI at day 20 revealed a massive subcutaneous lymphangiectasia, especially of the proximal limbs and the axilla but neither thoracic/abdominal masses nor abnormalities of the ductus thoracicus (Fig 1A). A diagnosis of congenital generalized lymphangiectasia was histologically and immunohistochemically confirmed (dilated lymphatic vessels, endothelial cells positive for CD31 and D2-40). The patient did not carry mutations in the CCBE1, FOXC2, and the FLT-4 genes, which have been identified to cause congenital lymphedema syndromes or diffuse lymphangiomatosis, respectively. Known etiologic factors such as chromosomal abnormalities or hematologic, cardiac, and metabolic

FIGURE 1
MRI of the thorax and abdomen at day 20 (A) and day 68 (B). Note the regression of the dilated lymphatic vessels in the axillae and groin. Chest radiographs at day 1 (C), day 25 (D), and at readmission when the girl was 6 months old (E) and 9 months old (F).
disorders as well as underlying infections were ruled out.

Recently, Ozeki et al. reported successful treatment of a 13-year-old boy with intractable diffuse lymphangiomatosis with propranolol. We hypothesized that propranolol might also be a therapeutic option in hydrops fetalis with congenital generalized lymphangiectasia. After written informed consent was obtained from the parents, propranolol treatment was initiated at day 25. Propranolol was gradually increased under continuous monitoring of the heart rate and blood pressure from 0.1 to 2 mg/kg per day, which was well tolerated. The visible lymphangiomatous lesions rapidly regressed within 14 days. MRI at day 68 confirmed a marked regression of the lymphangiectasia (Fig 1B). Sixteen days after start of the therapy, we were able to terminate mechanical ventilation and to reduce diuretic treatment. Plasma levels of vascular endothelial growth factor (VEGF) C and VEGF receptor 3 (VEGFR-3) (Fig 2), which were determined before and after propranolol administration, decreased with propranolol therapy (VEGF-C on day 0 of treatment, 609 pg/mL; day 15, 396 pg/mL; day 42, 345 pg/mL; VEGFR-3 on day 0 of treatment, 22 148 pg/mL; day 15, 7010 pg/mL; day 42, 8803 pg/mL). At the age of 10 weeks the patient was discharged from hospital and remained in good condition under treatment with propranolol during the subsequent months. The propranolol dose was increased corresponding to weight gain. At the age of 6 months, shortly after presenting with symptoms of a gastroenteritis, she developed a clinical relapse of the generalized lymphangiectasia and was readmitted to our hospital. By clinical examination, chest radiograph, and ultrasound we diagnosed generalized edema and pleural effusions. Due to the relapse of the pulmonary manifestation she required oxygen supplementation with a maximal flow rate of 2 to 3 L/minute. Although the symptoms resolved after escalation of the diuretic treatment, the patient still needed mild oxygen supplementation with a 0.5-L/minute flow rate at discharge 15 days later. Within the subsequent months the girl continued to require mild oxygen supplementation (0.25-L/minute flow rate). At the age of ~9 months, she was again admitted to our hospital with severe obstructive bronchitis due to a human metapneumovirus infection. She developed severe acute respiratory distress syndrome requiring mechanical ventilation and died 5 days after admission. Unfortunately, the parents refused autopsy. Considering the course of the disease and the divergent development of the lymphangiogenic factor levels we are not able to determine whether the pulmonary deterioration was due to the virus infections and/or a progression of the generalized lymphangiectasia.

**DISCUSSION**

Propranolol, which was incidentally found to have antiproliferative effects in infantile hemangiomas 5 years ago, has been established as a treatment of this disease. It is considered to cause vasoconstriction, inhibition of angiogenesis (among others, via a reduced expression of VEGF), and induction of apoptosis in capillary endothelial cells. The VEGF family plays a pivotal role in angiogenesis, vasculogenesis, and lymphangiogenesis. Whereas VEGF-A, the founding member of the VEGF family, also simply termed VEGF, is a potent growth factor for blood vessel endothelial cells, VEGF-C and its receptor VEGFR-3 are lymphangiogenic factors inducing lymphatic endothelial cell proliferation. Overexpression of VEGF-C in the skin of transgenic mice results in hyperplasia of cutaneous lymphatic vessels. Ozeki et al. reported a remarkable decrease in not-further-specified VEGF after administration of propranolol, supporting the hypothesis of an antiproliferative effect of propranolol in lymphangiomatosis. After previous investigations showing that inhibition of VEGF reduces lymphangiogenesis, propranolol was suggested to be a therapeutic option in the therapy for
diffuse lymphangiomatosis. In our patient, both factors markedly decreased after propranolol treatment within the first months. Although no reference parameters for VEGFs or receptors in preterm infants are available, the clinical course fits well with decreasing levels of VEGF-C and VEGFR-3 under propranolol therapy within the first months. The initial VEGF-C level was elevated compared with the few data available for healthy infants, but all of them referring to VEGF-A. Recently, Ozeki et al reported on propranolol therapy for pediatric lymphatic malformation. They found a decrease in VEGF-A, VEGF-C, and VEGF-D levels, all of which were elevated compared with controls before treatment with propranolol. Notably, in those subjects with an objective response, defined as tumor reduction >10% and <-50%, only VEGF-C levels appeared to remain low after treatment when compared with minimal responders (<10% tumor reduction) and nonresponders. Consequently, VEGF-C might be a suitable maker to evaluate the effect of propranolol in lymphatic malformations and generalized lymphangiectasia. Treatment efficiency in our patient was preserved until the girl was 6 months old.

When the patient relapsed, VEGF-C levels increased, whereas VEGFR-3 levels decreased. Considering that overexpression of VEGF-C in the skin of transgenic mice results in hyperplasia of cutaneous lymphatic vessels and that VEGFR-3 has been shown to be upregulated in lymphangiomas, an increase in both VEGF-C and VEGFR-3 levels might have been expected. Interpretation of our observations is difficult because, to our knowledge, VEGFR-3 serum levels have not yet been investigated in children.

Therefore, reference values in representative cohorts are required.

To our knowledge, the use of propranolol in the therapy for generalized lymphangiomatosis has exclusively been reported in a 13-year-old boy but not in infants of a younger age. For the first time, we describe propranolol treatment of generalized lymphangiectasia in a preterm infant. Treatment was safe and effective within several months. It remains to be shown whether propranolol is a treatment option for infants with generalized lymphangiectasia.

ACKNOWLEDGMENTS

We thank Professor R.C.M. Hennekamp and Dr M. Alders (Department of Clinical Genetics, Academic Medical Center, Amsterdam, Netherlands) for mutation analysis of the CCBEl gene and Professor P. Lohse (Institute for Laboratory Medicine, Singen, Germany) for mutation analysis of the FLT-4 and FOXC2 genes.

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*Pediatrics* 2014;133;e439; originally published online January 20, 2014; DOI: 10.1542/peds.2012-2087

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