Published in final edited form as:

Am J Med Genet A. 2006 February 15; 140(4): 368–372. doi:10.1002/ajmg.a.31093.

Familial Congenital Nonimmune Hydrops, Chylothorax and Pulmonary Lymphangiectasia

David A. Stevenson¹, Theodore J. Pysher², Robert M. Ward³, and John C. Carey¹

¹Division of Medical Genetics, Dept. of Pediatrics, University of Utah, Salt Lake City, 50 N. Medical Dr., Salt Lake City, Utah, USA

²Department of Pathology, University of Utah, Salt Lake City, 50 N. Medical Dr., Salt Lake City, Utah, USA

³Division of Neonatology, Dept. of Pediatrics, University of Utah, Salt Lake City, 50 N. Medical Dr., Salt Lake City, Utah, USA

Abstract

Pulmonary lymphangiectasia is an uncommon congenital anomaly, and familial occurrence has rarely been reported. We report on two sibs with bilateral pleural effusion/chylothorax and hydrops who died neonatally. One sib required prenatal intrauterine hemithoracic drainage. Autopsy confirmed congenital pulmonary lymphangiectasia (CPL) histologically in the first case.

Hydrops, characterized as subcutaneous edema and effusions in two or more body cavities, may be due to a variety of factors, but the co-occurrence of CPL in one of these sibs, although rare, supports the notion that chylothorax and hydrops may be caused by structural lesions of lymph channels. Although most cases of CPL are sporadic, the reported sibs support autosomal recessive inheritance, with intrafamilial variability of a lymphatic disorder on a genetic basis. Mutations in *VEGFR3* in families with Milroy disease, mutations of *FOXC2* in the lymphedema-distichiasis syndrome, and fatal chylothorax in $\alpha 9$ -deficient mice are potential candidate genes.

Keywords

chylothorax; congenital pulmonary lymphangiectasia; familial; hydrops

Introduction

Pulmonary lymphangiectasia is an uncommon, typically lethal, congenital vascular dysplasia characterized by an increased number of dilated pulmonary lymphatics in the subpleural, peribronchial, and interlobular septa. Respiratory distress is usually noted immediately after birth with frequent neonatal death [Albers and Wood, 1993].

Congenital pulmonary lymphangiectasia (CPL) is seen in anomalous pulmonary venous connection and several malformation syndromes including Noonan and Ullrich-Turner syndrome. Children without an associated disorder usually are a sporadic occurrence in their family, but rare familial occurrence has been reported. To our knowledge, four sets of sibs (one or more sibs have pulmonary lymphangiectasia or a related condition) have been documented. Jacquemont et al. [2000] described 3 siblings with variable findings of

hydrops, facial and lower limb edema, chylothorax, and congenital pulmonary lymphangiectasia (CPL). Njolstad et al. [1998] reported 3 sibs with prenatally diagnosed non-immune hydrops with pleural effusions. Only one sib was diagnosed with CPL. Moerman et al. [1993] reported on 2 sibs with chylothorax and pleural effusions. One had a CPL and non-immune hydrops with neonatal death, but there was limited information available on the other sib. The third familial report by Scott-Emuakpor et al. [1981] described two sibs with CPL.

Clinical Report

We report on two sibs with bilateral pleural effusion/chylothorax and hydrops with neonatal death. Clinical and pathologic findings are summarized in Table I.

Sib 1

This boy was born at 35 weeks of gestation to an 18-year-old primigravid woman. During the pregnancy she had pregnancy-induced hypertension. Consanguinity was not reported. Amniocentesis at 20 weeks showed a normal karyotype (46,XY).

The infant was delivered normally with Apgar scores of 1, 3 and 5 at one, 5 and 10 minutes, respectively. Aggressive resuscitation and mechanical ventilation were required and he underwent serial thoracotomies for persistent pleural drainage without improvement. He was diagnosed with non-immune hydrops and bilateral chylothorax. When he was switched to enteral feeding at age 4 weeks he began accumulating more pleural fluid and enteral feedings were discontinued one week later. He underwent a thoracic duct ligation without improvement.

Physical examination demonstrated an infant without other congenital anomalies (Fig. 1). Cryptorchidism was present. An echocardiogram showed a transitional type AV canal.

Support was withdrawn at 45 days of age and the infant died. At autopsy weight was 2780 g ($\approx 5^{\text{th}}$ centile), length was 48.5 cm ($\approx 10^{\text{th}}$ centile), and head circumference (OFC) was 33 cm ($\approx 5^{\text{th}}$ centile). Autopsy confirmed a transitional type AV canal with a partially cleft mitral valve, and CPL with numerous dilated lymphatics within the pleurae and interlobular septa upon microscopic examination (Fig. 2). The right lung weighed 37 g and the left 28 g (normal 40.6 $\pm$ 17.1 g). There were no other malformations.

Sib 2

The sister of patient 1 was born at 29 weeks of gestation. Pregnancy was complicated by premature rupture of membranes two weeks prior to birth. Hydrops and pleural effusions were diagnosed *in utero* and intrauterine placement of a pigtail catheter in the left hemithorax was performed. Upon delivery, the infant immediately had respiratory distress with hypoxia. She was given surfactant and antibiotics. She required mechanical ventilatory support and was diagnosed with non-immune hydrops, bilateral pleural effusion/chylothorax, and pulmonary hypoplasia. Paracentesis yielded 125 ml of serosanguinous fluid with 86% lymphocytes and bilateral chest tubes were placed. A chest radiograph showed very small lungs despite high ventilator pressures. Oxygen saturations continued to fall and she became bradycardic. The abdomen acutely increased in size, and an abdominal angiocatheter began to drain blood. The patient died at age two days.

At autopsy the infant was normally developed with appropriate morphometric measurements for 29 weeks of gestation (Fig. 3). Weight was 760 g ($\approx 10^{\text{th}}$ centile), length 41 cm ($\approx 75^{\text{th}}$ centile), and OFC 28.6 cm ($\approx 75^{\text{th}}$ centile). Grossly the heart was unremarkable. The abdominal cavity contained 42 cc of serosanguinous fluid and mucosal-associated lymphoid

tissue in the bowel was increased. Bilateral thoracic effusions were noted with the lymphocytosis characteristics of chylous effusion. The lungs were small (combined weight of 10.3 g, expected 23 +/- 12.6 g; lung:body weight ratio 0.019), but lung development was structurally normal for gestational age. There was moderate septal edema and congestion but no lymphatic dilatation or proliferation diagnostic of lymphangiectasia. The karyotype was 46,XX.

Discussion

CPL, chylothorax, and lymphedema may be manifestations of lymphatic abnormalities involving structural and developmental changes of the lymph channels. Sometimes these conditions are seen in isolation while at other times they are associated with other malformations. Lymphedema/generalized lymphatic dysplasia has been observed in at least 27 genetic syndromes listed by Allanson in her review of lymphatic circulation [1993]. Chylothorax and hydrops are observed in many genetic syndromes and pulmonary lymphangiectasia is seen frequently in total anomalous pulmonary venous return and, more rarely, in some malformation syndromes (eg. Noonan and Ullrich-Turner syndrome). CPL and congenital heart defects are associated with Noonan syndrome, and while hydrops in both patients distorts possible dysmorphic features, neither of our patients had posteriorly angulated ears. In addition, neither parent had short stature, known heart defects, or facial features consistent with Noonan syndrome.

Most cases of CPL are isolated and sporadic [Bellini et al., 2004]. One case of isolated CPL in a dizygotic twin has been reported [Baird et al., 1997]. They found placental abnormalities in the affected twin suggesting that maternal/placental factors may contribute to CPL. The pathogenesis of CPL is likely heterogeneous and may have maternal-fetal environment contributions. The mother of our patients did not have a known coagulation disorder and was otherwise healthy, but an unrecognized maternal condition cannot be ruled out as a contributing factor to the development of CPL in these sibs.

Familial occurrences of CPL are rare and to our knowledge only four families are documented [Jacquemont et al., 2000; Moerman et al., 1993; Njolstad et al., 1998; Scott-Emuakpor et al., 1981]. CPL was not uniform in 3 of the 4 previously reported families, but in those 3 families all had non-immune hydrops with pleural effusions and/or chylothorax. Findings of the previous families and our family are summarized in Table I.

Our patients, in addition to the previously reported familial cases, suggest that in some instances a spectrum of CPL with chylothorax has a genetic basis. There is clinical variability among the reported familial cases. CPL cannot be reliably diagnosed prenatally, and neonatally it is radiographically indistinguishable from chronic lung disease or pulmonary interstitial emphysema [Gilewski et al., 1996]. A definitive diagnosis of pulmonary lymphangiectasia is typically made histologically on lung biopsy [Albers and Wood, 1993]. The intrafamilial discordance of the histological presence of CPL in the reported familial cases (Table I) puts into question the utility of diagnosing CPL histologically. The co-occurrence of chylothorax (described in the reported familial cases) with CPL supports the thought that disordered lymphatic drainage is the basic defect leading to a secondary condition of CPL.

The pulmonary lymphatics are well developed by the end of 14 weeks of gestation and lymphangiectasis is a secondary dilation of previously normal lymphatics [Allanson, 1993; Noonan et al., 1970]. Regression of the lymphatics occurs after the 18-20th week of gestation and conditions preventing this regression may lead to CPL [Moerman et al., 1993]. However, the diagnosis of pulmonary lymphangiectasia does not provide cause. Noonan et

al. [1970] classified CPL into three categories suggesting possible causes after reviewing 3 new cases and 45 previously reported cases of pulmonary lymphangiectasis. The first group consisted of patients with dilated pulmonary lymphatics as part of a generalized form of lymphangiectasis with apparently less severe pulmonary involvement. The second group consisted of cases with obstruction to pulmonary venous flow and secondary dilatation of the lymphatics most likely acquired *in utero*. The third group was comprised of patients with a primary developmental defect of the lung lymphatics [Noonan et al., 1970]. The heart defects leading to pulmonary lymphangiectasia included total anomalous venous return, hypoplastic left heart, and obstructed pulmonary venous return [Albers and Wood, 1993; Noonan et al., 1970]. The first sibling we described had a transitional type AV canal. This heart defect did not cause significant obstruction to pulmonary venous return and was not thought to have been the primary cause of CPL in our patient.

Although most cases of CPL are sporadic, the reported familial cases support autosomal recessive inheritance of a lymphatic disorder with intrafamilial variability. Other lymph channel disorders provide insight into the pathophysiology of disorders involving the lymph system. Genes have been identified for some lymph channel disorders, which are discussed subsequently. They may be useful in identifying candidate genes for this apparent autosomal recessive condition.

Mutations in *FOXC2* patients have been reported in patients with the autosomal dominant lymphedema-distichiasis syndrome [Traboulsi et al., 2002], and families with hereditary lymphedema with overlapping phenotypes (variable findings of the Meige lymphedema syndrome, the yellow nail syndrome, and the lymphedema and ptosis syndrome) [Finegold et al., 2001]. *FOXC2* is a forkhead family transcription factor gene located at 16q24.3, and there is no apparent genotype-phenotype correlation [Evans et al., 2003, Ferrell, 2002].

Mutations in the vascular endothelial growth factor receptor-3 (*VEGFR3*) gene have been reported in families with Milroy disease, an autosomal dominant condition [Evans et al., 2003; Ferrell, 2002; Irrthum et al., 2000]. The vascular endothelial growth factor receptors are essential in angiogenesis and lymphangiogenesis. VEGF-C and VEGF-D have been shown to activate VEGFR-3 [Saaristo et al., 2002]. Recently, a study showed that local transfer of naked plasmid DNA encoding human VEGF-C resolves lymphedema and induces new lymphatic vessel growth in the mouse [Yoon et al., 2003], providing insights into potential therapeutic interventions in lymph channel disorders.

Fatal bilateral chylothorax has been reported in mice lacking the integrin $\alpha 9\beta 1$ (a receptor for the extracellular matrix proteins osteopontin and tenascin C and the cell surface immunoglobulin vascular cell adhesion molecule-1) [Huang et al., 2000]. Mice homozygous for a null mutation in the $\alpha 9$ subunit gene died of respiratory failure due to bilateral chylothorax within 6 to 12 days after birth. Edema and lymphocytic accumulation were most prominent near the lymphatic vessels. The phenotype in this mouse is similar to that observed in the presented sibs. Mutations in genes encoding proteins that impair the expression or function of this adhesion receptor may be causative in our reported family.

Recent advances in gene therapy involving the vascular endothelial growth factor receptors in animals are encouraging [Saaristo et al., 2002; Yoon et al., 2003], and the mouse with fatal chylothorax gives hope for a potential candidate gene [Huang et al., 2000]. Further research to identify a gene and better understand the pathophysiology may lead to effective therapy in this highly morbid condition.

Acknowledgments

We thank the family for their help and participation. This research was carried out with support in part from a Public Health Services research grant #M01-RR00064 from the National Center for Research Resources, the Children's Health Research Center at the University of Utah, and the Clinical Genetics Research Program at the University of Utah. Dr. Stevenson was supported in part by NINDS grant #1 K23 NS052500-01. Dr. Ward was supported in part by NICHD grant 1 U10 HD045986-01.

References

- Albers, GM.; Wood, RE. Lower Respiratory Organs. In: Stevenson, RE.; Hall, JG.; Goodman, RM., editors. *Human Malformations and Related Anomalies*. New York, Oxford: Oxford University Press; 1993. p. 361-362.
- Allanson, JE. Lymphatic circulation. In: Stevenson, RE.; Hall, JG.; Goodman, RM., editors. *Human Malformations and Related Anomalies*. New York, Oxford: Oxford University Press; 1993. p. 271-287.
- Baird AR, Nwosu CR, Crichton F, Carey FA, Lang S, Agustsson P. Isolated congenital pulmonary lymphangiectasis in a dizygotic twin pregnancy. *J Obstet Gynaecol*. 1997; 17:492-494. [PubMed: 15511936]
- Bellini C, Mazzella M, Campisi C, Taddei G, Mosca F, Tomà P, Villa G, Boccardo F, Sementa AR, Hennekam RC, Serra G. Multimodal imaging in the congenital pulmonary lymphangiectasia-congenital chylothorax-hydrops fetalis continuum. *Lymphology*. 2004; 37:22-30. [PubMed: 15109074]
- Evans AL, Bell R, Brice G, Comeglio P, Lipede C, Jeffery S, Mortimer P, Sarfarazi M, Child AH. Identification of eight novel *VEGFR-3* mutations in families with primary congenital lymphoedema. *J Med Genet*. 2003; 40:697-703. [PubMed: 12960217]
- Ferrell RE. Research perspectives in inherited lymphatic disease. *Ann N Y Acad Sci*. 2002; 979:39-51. [PubMed: 12543715]
- Finegold DN, Kimak MA, Lawrence EC, Levinson KL, Cherniske EM, Pober BR, Dunlap JW, Ferrell RE. Truncating mutations in *FOXC2* cause multiple lymphedema syndromes. *Hum Mol Genet*. 2001; 10:1185-1189. [PubMed: 11371511]
- Gilewski MK, Statler CC, Kohut G, Toriello HV. Congenital pulmonary lymphangiectasia and other anomalies in a child: provisionally unique syndrome? *Am J Med Genet*. 1996; 66:438-440. [PubMed: 8989463]
- Irrthum A, Karkkainen MJ, Devriendt K, Alitalo K, Vikkula M. Congenital hereditary lymphedema caused by a mutation that inactivates VEGFR3 tyrosine kinase. *Am J Hum Genet*. 2000; 67:295-301. [PubMed: 10856194]
- Jacquemont S, Barbarot S, Bocéno M, Stalder JF, David A. Familial congenital pulmonary lymphangiectasia, non-immune hydrops fetalis, facial and lower limb lymphedema: confirmation of Njolstad's report. *Am J Med Genet*. 2000; 93:264-268. [PubMed: 10946350]
- Moerman P, Vandenberghe K, Devlieger H, Van Hole C, Fryns JP, Lauweryns JM. Congenital pulmonary lymphangiectasis with chylothorax: a heterogeneous lymphatic vessel abnormality. *Am J Med Genet*. 1993; 47:54-58. [PubMed: 8368253]
- Njolstad PR, Reigstad H, Westby J, Espeland A. Familial non-immune hydrops fetalis and congenital pulmonary lymphangiectasia. *Eur J Pediatr*. 1998; 157:498-501. [PubMed: 9667408]
- Noonan JA, Walters LR, Reeves JT. Congenital pulmonary lymphangiectasis. *Am J Dis Child*. 1970; 120:314-319. [PubMed: 5493829]
- Saaristo A, Karkkainen MJ, Alitalo K. Insights into the molecular pathogenesis and targeted treatment of lymphedema. *Ann N Y Acad Sci*. 2002; 979:94-110. [PubMed: 12543720]
- Scott-Emuakpor AB, Warren ST, Kapur S, Quiachon EB, Higgins JV. Familial occurrence of congenital pulmonary lymphangiectasia: genetic implications. *Am J Dis Child*. 1981; 135:532-534. [PubMed: 7234788]
- Traboulsi EI, Al-Khayer K, Matsumoto M, Kimak MA, Crowe S, Wilson SE, Finegold DN, Ferrell RE, Meisler DM. Lymphedema-distichiasis syndrome and *FOXC2* gene mutation. *Am J Ophthalmol*. 2002; 134:592-596. [PubMed: 12383817]

Yoon YS, Murayama T, Gravereaux E, Tkebuchava T, Silver M, Curry C, Wecker A, Kirchmair R, Hu CS, Kearney M, Ashare A, Jackson DG, Kubo H, Isner JM, Losordo DW. VEGF-C gene therapy augments postnatal lymphangiogenesis and ameliorates secondary lymphedema. *J Clin Invest*. 2003; 111:717–725. [PubMed: 12618526]

Figure 1.
Photograph of sibling #1.

Figure 2.
Photograph of sibling #2.

Figure 3.
Histology of post-mortem lung tissue in sibling #1 showing numerous dilated lymphatics within the subpleural and interlobular septa.

Table 1

Clinical and Pathologic Findings in Familial Cases

Finding	This Family			Njolstad et al.			Jacquemont et al.			Scott-Emuakpor et al.		Moerman et al.	
	Sib 1	Sib 2		Sib 1	Sib 2	Sib 3	Sib 1	Sib 2	Sib 3	Sib 1	Sib 2	Sib 1	Sib 2
Gender	M	F		M	F	M	F	F	F	F	F	M	F
Gestational age	38 wks	29 wks		34 wks	34 wks	30 wks	term	32 wks	24 wks	term	term	30 wks	?
Pleural effusions	+	+		+	+	+	+	+	+	?	?	+	+
Chylothorax	+	+		?	?	+	?	+	?	?	?	+	+
Nonimmune hydrops	+	+		+	+	+	-	+	+	?	?	+	?
Normal karyotype	+	+		+	+	?	?	?	+	?	+	+	?
Heart defect	+	-		-	-	?	-	-	-	-	-	-	?
CPL histologically	+	-		-	?	+	?	-	+	+	+	+	?
Neonatal demise/stillbirth	+	+		+	-	+	-	-	+	+	+	+	-