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Review

Congenital pulmonary lymphangiectasis

Friedrich Reiterer [1,*], Karin Grossauer [1], Nicholas Morris [1], Sabine Uhrig [2], Bernhard Resch [1,3]

[1] Division of Neonatology, Department of Paediatrics, Medical University of Graz, Austria
[2] Institute of Human Genetics, Medical University of Graz, Austria
[3] Research Unit for Neonatal Infectious Diseases and Epidemiology, Medical University of Graz, Austria

EDUCATIONAL AIMS

- To present an overview of the origin of congenital pulmonary lymphangiectasis (CPL) and to discuss the different classification systems.
- To discuss the clinical course of CPL and the possibility of long term survival even in cases with severe neonatal onset.
- To give information on current diagnostic modalities
- To demonstrate the therapeutic options regarding prenatal and postnatal management
- To emphasize the importance of genetic counseling.

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SUMMARY

Congenital pulmonary lymphangiectasis (CPL) is a rare vascular malformation causing dilated lymph vessels and disturbed drainage of lymph fluid. Based on the pathogenesis and clinical phenotype it can be classified as primary or secondary CPL.

Associated genetic syndromes with or without lymphedema, familial occurrence and gene mutations have been described. In utero, it may present as non-immune hydrops with pleural effusions. At birth neonates may have respiratory failure due to chylothorax and pulmonary hypoplasia, causing very high short term mortality rates. Other cases may become symptomatic any time later in childhood or even during adult life. CPL is usually diagnosed based on the combination of clinical signs, imaging and histological findings. Open-lung biopsy is considered the gold standard for the diagnosis of CPL. Treatment is primarily supportive featuring aggressive mechanical ventilation and the management of problems associated with congenital chylothorax including chest-drainage, medium-chain triglycerides (MCT) diet, and octreotide.

INTRODUCTION

Congenital pulmonary lymphangiectasis (CPL) is a rare vascular disorder characterised by dilatation of lymphatic vessels in multiple areas of the lungs including subpleural, interlobar, perivascular, and peribronchial regions.

The original classification by Noonan et al. [1] divided pulmonary lymphangiectasis (PL) into three groups: 1) general lymphangiectasis with primarily intestinal involvement and less severe pulmonary disease, 2) secondary PL due to pulmonary venous obstruction (often associated with congenital heart disease), and 3) primary pulmonary lymphangiectasis. This classification has been modified and, on the basis of improved clinical characterization and advances in neonatal intensive care, been divided into two major categories, defined as primary and secondary CPL (Figure 1) [2,3].

Connell et al. [4] created a classification and diagnostic algorithm for primary lymphatic dysplasia based not simply on the age of onset of the lymphedema but also the sites affected and the presence of associated features. Considering CPL as being an inherent developmental abnormality of the lymphatic system, primary CPL fits into the category of systemic lymphatic problems persisting beyond the neonatal period or manifesting at any age thereafter (with pre- or postnatal onset) that further include

* Corresponding author. Division of Neonatology, Department of Paediatrics, Medical University of Graz, Auenbruggerplatz 34/2, 8036 Graz, Austria.
Tel.: +43 316 385 84558; fax: +43 316 385 12678.
E-mail address: friedrich.reiterer@medunigraz.at (F. Reiterer).

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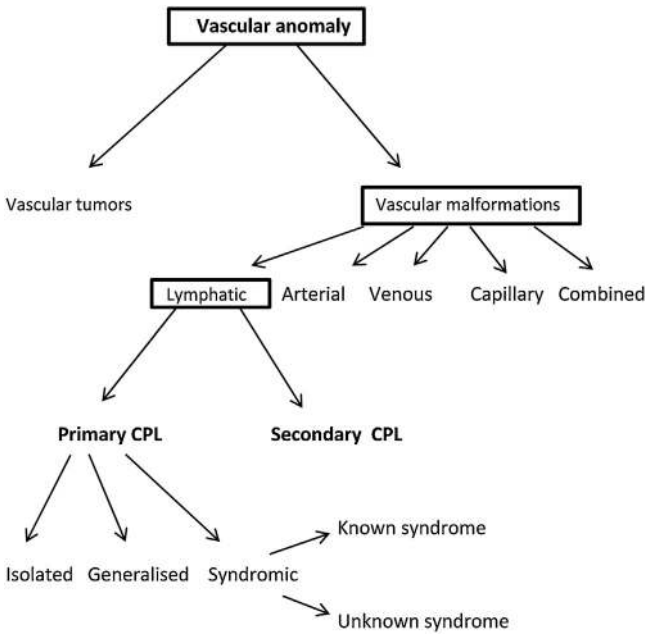

Figure 1. Classification of congenital pulmonary lymphangiectasis.

hydrops fetalis, chylous ascites, intestinal lymphangiectasis, pleural and pericardial effusions, and pulmonary lymphangiectasis.

Secondary PL comprises a heterogeneous group of conditions including hypoplastic left heart syndrome, pulmonary vein atresia, congenital mitral stenosis, cor triatum, and thoracic duct agenesis all causing obstruction and extravasation.

HISTORY

CPL was first described by Virchow in 1856 [5]. Until 1968 a total of 38 cases had been reported in the literature, most of these cases were reported in journals of pathology, 13 cases had been studied from a radiological viewpoint [5–20]. In 1970 Noonan et al. [1] reported on three cases of CPL who had undergone cardiac catheterization and had post-mortem injection studies demonstrating dilated pulmonary lymphatics. Noonan et al summarized all 45 known cases of CPL, added their own 3 cases and divided them into three groups as follows: 5 cases with a generalized form of lymphangiectasis (lymphedema with intestinal lymphangiectasis), 13 cases with lymphangiectasis secondary to pulmonary venous hypertension or obstruction, and 30 cases with primary pulmonary lymphangiectasis. Five of the 48 patients survived for over one month but no longer than 16 months and one patient was still alive at the age of 5 years. In 1971 France and Brown [21] reported on the features of 11 cases of CPL who had died during the neonatal period. Seven were associated with total anomalous pulmonary venous drainage. In 1972 [22], the British Medical Journal stated, that one case of CPL could be expected in every 170 postmortem examinations. Thus, a greater awareness of the condition should lead to its more frequent diagnosis in the postmortem room and perhaps also in life. "But unfortunately", the article concludes, "it seems doubtful whether anything much can be done for this condition, at least in its more severe form."

In 1977, the December volume of the Proceedings of the Royal Society of Medicine included "chylothorax and congenital pulmonary lymphangiectasia" in a classification system of causes of delayed respiratory distress in infancy. The author added CPL to the primary pulmonary causes separating them from extrapulmonary causes of respiratory distress starting more than one week after birth in infants who had had nil, or only transient and minor, respiratory problems immediately after birth [23]. The first case of CPL associated with pleural effusions was reported in 1984, with a suggestion of disordered lymphatic drainage being the cause [24]. Scalzetti et al. [25] published a review on developmental lymphatic disorders of the thorax and characterized four major types that affect the thorax: 1) lymphangiectasis, characterized by congenital anomalous dilatation of pulmonary lymph vessels; 2) localized lymphangioma, a rare and benign, usually cystic lesion characterized by mass like proliferation of lymph vessels; 3) diffuse lymphangioma: a proliferation of vascular, mainly lymphatic tissue in which visceral and skeletal involvement are common; and 4) lymphangioleiomyoma, which involves a haphazard proliferation of smooth muscle in the lungs and dilatation of lymphatic tissue. These characteristic findings could be seen both with radiographic studies as well as with histological evaluation. In 2003 Hagmann and Berger [26] stated that CPL is a uniformly fatal disease when it manifests in the newborn period. Since then, first reports of long-term survival have been published [27–29]. In 2006 for the first time it was speculated that endothelial nitric oxide synthesis (by immunohistochemistry) may play an important role in the pathogenesis of CPL as it was found to be present and upregulated in the endothelial lining of dilated lymphatic vessels [30].

DISEASE NAME AND EPIDEMIOLOGY

Bellini et al. [2] named several disease names as synonyms including pulmonary lymphangiectasia, pulmonary cystic lymphangiectasis, and pulmonary lymphangiomatosis. The latter is a rare disease characterized by diffuse infiltration of lymphangiomas in the lung, bone, and other tissues and is therefore, quite different to CPL [31]. The word "-ectasis" comes from the Greek word "ektasis"; meaning dilated, expanded, distended, extension. Thus, in our opinion the preferential wording is pulmonary lymphangiectasis as used by Noonan et al. [1].

The true incidence of CPL is difficult to estimate as far as only case reports and/or small case series have been published. A very recent report on the histopathological spectrum of congenital pulmonary developmental disorders stated that out of 2,155 stillbirth/neonatal autopsies there were 105 cases of pulmonary hypoplasia, two cases of CPL, two cases of extralobar sequestration, and three cases of congenital pulmonary airway malformation [32]. This data would suggest that approximately one in a thousand either stillborns or neonatal deaths is to some degree attributable to CPL, and is not consistent with significantly higher estimates reported in a review paper by Bellini et al. [2]. Familial occurrence of CPL is rare and only six affected families have been documented in the literature [33].

Embryology and Pathological Physiology

During embryonic development, blood vessels originate from mesodermally derived endothelial cell precursors (vasculogenesis), and these vessels grow and remodel into the mature network by endothelial sprouting and splitting (angiogenesis) [34]. The lymphatic vasculature appears after the blood vasculature forms, and this was the first indication that lymphatics might originate from the blood vasculature. Florence Sabin [35,36] proposed the most widely accepted model of lymphatic vasculature development almost 110 years ago. By injecting dye into pig embryos she proposed that endothelial cells bud from veins to form primary lymphatic sacs.

The lymph vessels grow during the ninth week. Between the twelfth and the sixteenth week of fetal life the pulmonary lymphatic tissue is well developed. During the 14th week of life lymph vessels form wide lymph trunks in the connective tissue which divide the parenchyma of the lung into distinct lobules.

Later, by the 20th week of life, the channels become narrower and the surrounding connective tissue diminishes [1].

Lawrence [18] expressed the belief that CPL stems from a continued growth of these tissues past the fetal stage. This theory, postulating that lymphangiectasis is due to a developmental error in which the normal regression of connective tissue elements fails to occur after the 16th week of life, appears to be better supported than that of Giammalvo [19] who postulated that this anomaly results from a failure or delay in linkage of isolated lymphatic spaces. Theros [10] correlated the pathological with the radiological features of CPL. On examination the lungs are bulky and inelastic with large cystic spaces in the subpleural area. On sectioning, cystic lymphatic areas are also found peribronchially and in the interlobular septa. This results in a honeycomb appearance. Microscopically, an increase in fibrous tissue may be seen in addition to the dilated cystic lymphatic spaces. The surrounding alveoli are nearly collapsed and airless, although there may be bronchiolar ectasis.

CLINICAL PRESENTATION AND DIAGNOSIS

CPL can present in the antenatal period as non-immune hydrops fetalis with hydrothorax, often in combination with polyhydramnios. Associated congenital and or chromosomal anomalies may be detected and are noticed frequently in aborted fetuses and non-survivors of CPL [28].

Clinical presentation at birth is often characterized by severe respiratory distress due to unilateral or bilateral pleural effusions, pulmonary hypoplasia and surfactant deficiency in combination with prematurity, leading to intubation and mechanical ventilation and even extracorporeal membrane oxygenation [37]. This is especially the case with primary CPL limited to the lung, which used to be considered a uniformly fatal disease when it manifests in the neonatal period [26]. Increased survival in this subgroup of CPL patients may be the consequence of advances in perinatal care including improvements in neonatal respiratory management [38,39].

Patients with generalized lymphangiectasis usually have less pulmonary involvement but develop more subcutaneous edema and visceral effusions, as described for some congenital genetic lymphedema syndromes [40,41].

The neonatal course may be complicated by persistent visceral chylous effusions, mainly chylothorax, ventilator dependency, anasarca, arterial hypotension, heart failure, secondary pulmonary hypertension, nosocomial infections and neonatal death, usually as a consequence of progressive respiratory failure due to pulmonary hypoplasia. CPL can also manifest later in the neonatal or postneonatal period or even as in some cases in childhood or adolescence or even in adult life [3,42]. It will usually present with respiratory symptoms like persistent tachypnea, recurrent cough or wheeze or airway infections. In patients with an early diagnosis of CPL and without significant associated congenital anomalies follow up studies have shown that long-term survival can be expected [28,43] with improving respiratory status. In lung function tests, restrictive and obstructive patterns have been described with relative stability over time [43]. Additionally, other medical problems including poor growth, gastro-esophageal reflux or motor developmental delay [3,29] may be present.

Diagnosis of CPL is most often based on clinical signs together with imaging and histological findings either from autopsy or open-lung biopsy. Open-lung biopsy, considered the gold standard for diagnosis, may also be helpful in the differential diagnosis of other forms of pulmonary lymphatic dilatation or interstitial lung diseases. Biopsy has not been uniformly reported in all surviving patients with the diagnosis of CPL, partly due to spontaneous improvements in their clinical condition [29,43–45]. Macroscopic and histologic examinations may show hypoplastic lungs with an irregular surface, scattered nodular changes along the visceral pleura, dilated or cystic intrapulmonary lymphatics without proliferation and thickened interlobular connective tissue [26,46,47]. On immuno-histochemical stains flat cells lining the thin wall of lymphatic spaces have been shown to be positive for several antibodies, like CD31, CD-34, and D2-40 (Figure 2), indicating their endothelial nature [47,48]. Imaging findings for CPL on chest radiography and high-resolution computed tomography (Figures 3 and 4) are usually described as reticulo-nodular with increased interstitial markings or thickening, likely presenting dilated pulmonary lymphatics, that tend to regress after infancy, and bilateral pulmonary hyperinflation, that generally increases with age [44]. Although not specific, these findings may add to the diagnosis of CPL, especially in the absence of a histological evaluation.

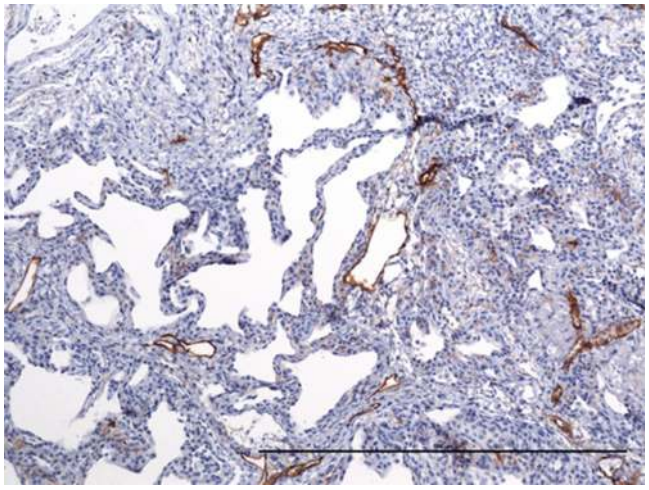

Figure 2. Histology of the lung of a neonate with trisomy 21 from our division suffering from syndromic CPL. Immunohistochemistry was performed using antibodies against podoplanin highlighting all lymphatic vessels, including cystic dilated ones in brown (bar 500 μm).

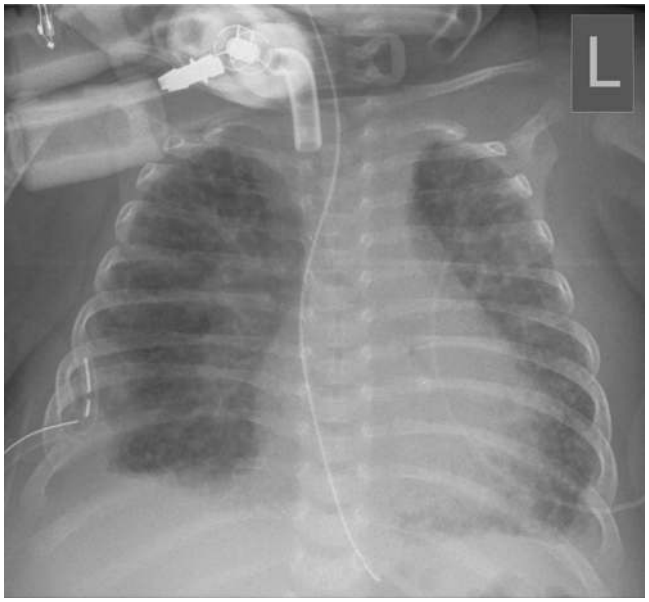

Figure 3. Chest-radiograph of a 10 weeks old infant from our division with histologically proven CPL [55]. Bilateral reticulo-nodular interstitial pattern, confluent in the perihilar region, pleural effusions, right-sided pleural drain, tracheostoma.

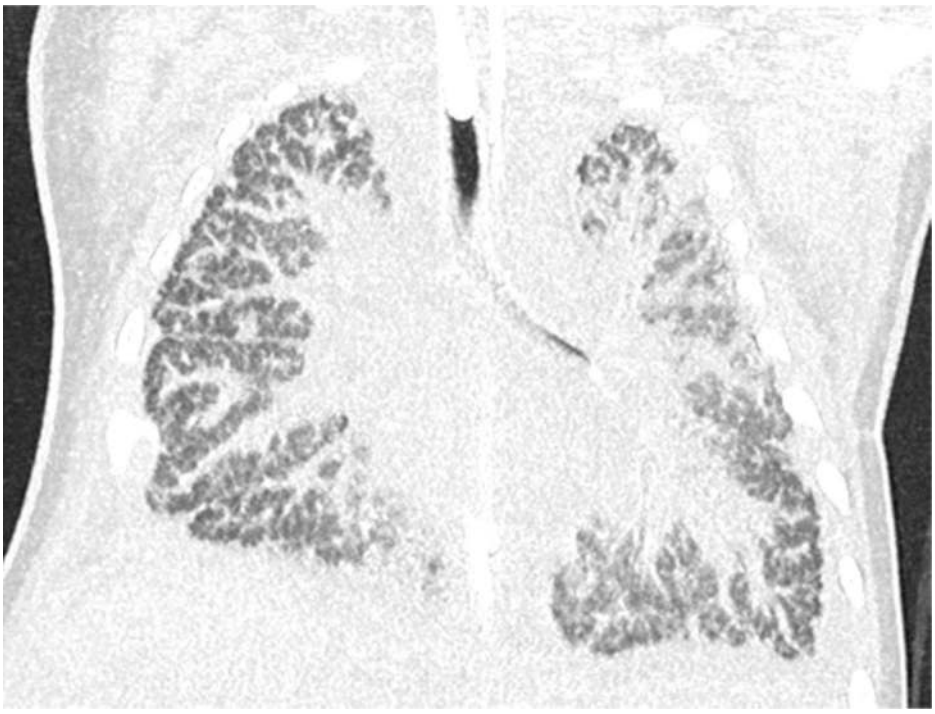

Figure 4. High-Resolution CT of thorax of the same patient [55].
Bilateral streaky, patchy parenchymal consolidation areas suggesting interstitial infiltrates.

Lymphoscintigraphy may be a further non-invasive means of identifying lymph vessel abnormalities, although rarely reported. Bellini et al. [49] used radionuclide lymphoscintigraphy of the hands and feet in a preterm neonate, presenting as non-immune hydrops fetalis with congenital chylothorax (CC) and CPL to demonstrate an abnormal drainage of the lower limb and the thoracic duct. The authors speculated that "reverse-flow" in the thoracic duct might have resulted in accumulation of lymph fluid within the pleural and pulmonary lymphatic system adding an interesting aspect to the pathogenesis of primary CPL and CC already discussed by Moerman et al. [50].

THERAPEUTIC OPTIONS

Due to the variable clinical presentation and course of CPL there is no uniform, standardized management strategy. Prenatal treatment of fetal chylothorax by thoracocentesis, thoraco-amniotic shunting or medical pleurodesis should be considered to prevent severe pulmonary hypoplasia and hydrops, especially when the degree of pulmonary and cardiac compression is considered significant [37,51–55]. These treatment modalities may also allow delivering the fetus closer to term. The rational for thoraco-amniotic shunting, the most common procedure for treatment of fetal chylothorax in CC, has been discussed recently in several reports [56–58].

Postnatal treatment of CPL is primarily supportive including aggressive mechanical ventilation, surfactant administration, thoracocentesis, ECMO, cardio-circulatory support with inotropes, diuretics, total parenteral nutrition (TPN) and substitution of losses of electrolytes, coagulation factors and immunoglobulines associated with CC. The management of persistent, refractory CC in CPL might be a challenge in the neonatal course requiring prolonged conservative and or surgical interventions. A low oral fat diet with medium-chain triglycerides (MCTs), which lessens the intestinal lymph flow and pressure in the gut by absorption of fat directly to the portal blood stream, has been shown to be a valid option for patients with primary intestinal lymphangiectasis [59], and has also be used in patients with CC and CPL.

Octreotide, a somatostatin analog, is a therapeutic option if chylothorax persists after a failed trial of exclusive TPN or MCT diet. Given subcutaneously or intravenously it is thought to have a direct effect on the vascular somatostatin receptor level with vasoconstriction of the splanchnic circulation, thereby decreasing chyle production, intestinal lymphatic volume and flow in the thoracic duct [60]. Treatment trials with Octreotide for patients with CPL and CC are only reported in uncontrolled case studies [41,60–62] with no clear and consistent effect on pleural effusions. Adverse side effects like gastrointestinal intolerance or transient hypothyroidism have to be considered. In one study pulmonary hypertension was described as a common problem in neonates with CC treated with intravenous Octreotide [60]. A multicenter randomized controlled trial is needed to assess the efficacy and safety of Octreotide in CC and CPL [63].

An interesting new therapeutic medical agent for lymphatic malformations might be Sirolimus, an orally given immunosuppressive drug with antiangiogenic and antiproliferative properties. Recently, it has been reported as being successful in treating complicated, life-threatening non-proliferative vascular anomalies in 6 patients with an age ranging from 7 months to 14 years, having mainly microcystic lymphatic malformations and visceral chylous effusions [64]. To our knowledge it has not yet been reported in treating CPL. Just recently we successfully used Sirolimus for the first time to treat a neonate with trisomy 21, CC and histologically proven CPL after attempts to treat with TPN, MCTs, and Octreotide had failed to consolidate chylous effusions (unpublished observation). Another treatment approach that might be considered in CPL and refractory CC is chemical pleurodesis with intrapleural instillation of different agents like OK-432 [65], minocycline [66], povidone -iodine [67], and autologous blood [46], inducing an inflammatory response in the pleural cavity leading to pleural fibrosis and sclerosis.

Finally surgical interventions such as pleurectomy and pleurodesis or thoracic duct ligation may be worth considering in

Table 1
Syndromes in which pulmonary lymphangiectasis has been described

Syndrome	Inheritance	Gene / chromosome	OMIM catalog
Turner		45,X	
Down		47,+21	
Phelan McDermid		22q13.3 deletion or SHANK3 mutation	
Njolstad	AR or XR	unknown	236750
primary congenital pulmonary lymphangiectasis	AR or XR	unknown	265300
Noonan	AD	PTPN11, KRAS, SOS1, RAF1 and others	163950, 190070,182530, 164760
Cardio-facio-cutaneous	AD	BRAF,KRAS,MAP2K1, MAP2K2	115150
Costello	AD	HRAS	190020
Hennekam	AR	CCBE1 and unknown	235510
Nonne-Milroy lymphedema	AD	FLT4 (VGFR3)	153100
lymphedema-distichiasis	AD	FOXC2	153400
Yellow nail	AD	FOXC2 and unknown	153300
hypotrichosis-lymphedema-telangiectasia	AR	SOX18	607823
Lymphedema-Hypoparathyroidism	AR or XR	unknown	247410
Urioste	AR or XR	unknown	235255
Lymphedema hypoparathyroidism	AR or XR	unknown	247410
German	AR	unknown	231080
Opitz G/BBB	XR	MID1	300552

AR = autosomal recessive; AD = autosomal dominant, XR = X-chromosomal recessive, OMIM® = Online Mendelian Inheritance in Men

extreme cases when all conservative treatment trials are failing to minimize further lung injury from prolonged mechanical ventilation [68].

GENETIC COUNSELING

Pulmonary lymphangiectasis is heterogeneous and most cases occur sporadically [2,3,28]. A male preponderance has been reported [2,28]. PL can be associated with chromosomal anomalies including Turner, Down and Phelan McDermid Syndrome [28,50,69]. Therefore a chromosomal disorder should be ruled out by array-CGH analysis on a high resolution platform (Table 1). In the primary pulmonary form of lymphangiectasis disease is confined to the lungs like in CPL (OMIM 265300) or Njolstad syndrome (OMIM 236750). The genetic background of these syndromes is unknown but rare recurrence in siblings suggests an autosomal-recessive or X-linked recessive inheritance [55,70,71]. Dominant inheritance with reduced penetrance has also been discussed [28]. There are syndromic forms where PL is associated with multiple unrelated congenital anomalies. In this category the RASopathies (Noonan syndrome, Cardio-Facio-Cutaneous syndrome, Costello syndrome) constitute a major part [2,28,68] and patients should be evaluated clinically for signs of these syndromes. If a RASopathy phenotype is suspected, a genetic evaluation should be performed to confirm the diagnosis on a molecular basis. PL can be part of generalized lymphatic dysplasia like in Hennekam syndrome (OMIM 235510), therefore intestinal involvement should be ruled out. If there are signs of intestinal lymphangiectasis, we recommend testing for mutations in *CCBE1*, the only gene known to date for Hennekam syndrome [71]. Because the clinical diagnosis of Nonne-Milroy disease (OMIM 153100) or lymphedema associated with distichiasis (153400) can be very difficult due to variable gene expression [40,72], mutation analysis of *VEGFR3 (FLT4)* and *FOXC2* should be considered in cases where clinical evaluation does not support one of the other above mentioned rare syndromes.

CONCLUSION

With the advances in perinatal care, including several preventive and therapeutic options to manage respiratory insufficiency, CPL, especially in the primary form, is now more frequently diagnosed and associated with even long-term-survival. Diagnosis is based on the clinical picture, multimodal imaging and open-lung biopsy, the latter still being the gold standard for the definitive diagnosis. Despite decreased mortality, morbidity may still be high and interdisciplinary long-term follow up is necessary. Most CPL cases are sporadic with male predominance but one should always consider an underlying syndrome and in most cases consult a geneticist.

Acknowledgement

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PRACTICE POINTS

- Severe neonatal onset of CPL is not necessarily associated with a fatal course of the disease
- Gold standard of diagnosis is still lung biopsy with subsequent immuno-histochemical staining applying antibodies specific for lymphatic vessels
- An interesting new therapeutic medical agent for lymphatic malformations might be Sirolimus reported as being successful in treating complicated, life-threatening non-proliferative vascular anomalies

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