Paediatric Respiratory Reviews 15 (2014) 275–280

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

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.

ARTICLE INFO

Keywords:
Congenital pulmonary lymphangiectasis
Review
Classification
Diagnosis
Therapeutic options
Genetic counselling

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).

http://dx.doi.org/10.1016/j.prrv.2014.05.002
1526-0542/

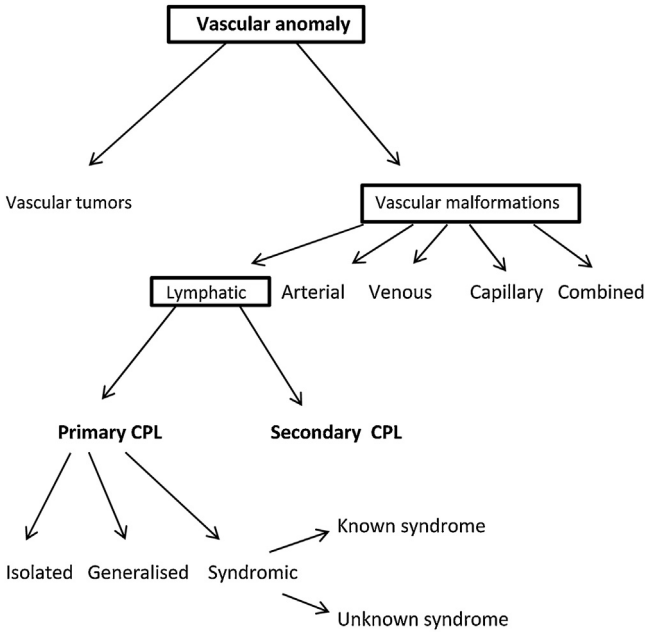

Figure 1. Classification of congenital pulmonary lymphangiectasis.

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.