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No Pathogenic *DICER1* Gene Variants in a Cohort Study of 28 Children With Congenital Pulmonary Airway Malformation

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ABSTRACT

Background: Distinguishing congenital pulmonary airway malformations (CPAMs) from pleuropulmonary blastoma (PPB) can be challenging. Previously diagnosed patients with CPAM may have been misdiagnosed and we may have missed *DICER1*-associated PPBs, a diagnosis with important clinical implications for patients and their families. To gain insight in potential misdiagnoses, we systematically assessed somatic *DICER1* gene mutation status in an unselected, retrospective cohort of patients with a CPAM diagnosis.

Methods: In the Amsterdam University Medical Center (the Netherlands), it has been standard policy to resect CPAM lesions. We included all consecutive cases of children (age 0–18 years) with a diagnosis of CPAM between 2007 and 2017 at this center. Clinical and radiographic features were reviewed, and *DICER1* gene sequencing was performed on DNA retrieved from CPAM tissue samples.

Results: Twenty-eight patients with a surgically removed CPAM were included. CPAM type 1 and type 2 were the most common subtypes (n = 12 and n = 13). For 21 patients a chest CT scan was available for reassessment by two pediatric radiologists. In 9 patients (9/21, 43%) the CPAM subtype scored by the radiologists did not correspond with the subtype given at pathology assessment. No pathogenic mutations and no copy number variations of the *DICER1* gene were found in the DNA extracted from CPAM tissue (0/28).

Conclusions: Our findings suggest that the initial CPAM diagnoses were correct. These findings should be validated through larger studies to draw conclusions regarding whether systematic *DICER1* genetic testing is required in children with a pathological confirmed diagnosis of CPAM or not.

Level of Evidence: Level IV.

Abbreviations: CCAM, congenital cystic adenomatoid malformation; CPAM, congenital pulmonary airway malformations; CT, computed tomography; CTA, CT angiography; LLL, left lower lobe; LUL, left upper lobe; MRI, magnetic resonance imaging; OS, overall survival; PPB, pleuropulmonary blastoma; RML, right middle lobe; RUL, right upper lobe; SNPs, single nucleotide polymorphisms.

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1. Introduction

Congenital lung malformations are a group of benign developmental pulmonary anomalies that include bronchopulmonary sequestration, bronchogenic cysts, congenital lobar emphysema, and congenital pulmonary airway malformations (CPAMs), previously known as congenital cystic adenomatoid malformation (CCAM) [1]. Although rare, CPAM is the most common congenital lung malformation. The prevalence is estimated at 1.19/10,000 fetuses according to the European EUROCAT registry [2]. CPAM can be divided into five subtypes (type 0–4), which are thought to originate at different stages of lung development and have different radiologic appearances and pathologic characteristics (Supplementary Table S1) [3–6]. CPAMs are usually suspected antenatally, during prenatal ultrasonography [7]. The majority of infants with prenatally suspected CPAM are asymptomatic at birth, but some may develop symptoms, such as dyspnea, pneumonia and pneumothorax [7,8]. While surgery is considered the cornerstone treatment for symptomatic patients, the management of asymptomatic lesions remains controversial since the natural history of CPAM is still unclear [7,9–12]. One of the arguments for early resection of asymptomatic CPAMs is, the possibility that the lung lesion is not a CPAM but instead a (pre)malignant lung lesion, such as pleuropulmonary blastoma (PPB) [9].

Pleuropulmonary blastoma (PPB) is a rare dysembryonic malignant lesion in the lung that is classified into three subtypes. The morphologic spectrum ranges from a purely cystic lesion (type I), usually diagnosed in the first year of life or even prenatally, to a mixed cystic and solid tumor (type II), and purely solid tumor (type III) (Supplementary Table S2) [13–16]. Type I PPB presents with incidental X-ray discovery or respiratory distress with pneumothorax due to the presence of air-filled cysts. Type I PPB, with a 5-year overall survival (OS) of 89%, can progress to the more aggressive type II and type III PPB, with a 5-year OS of 71% and 53%, respectively [13]. PPB type I is treated with complete surgical resection; in case of incomplete resection or intraoperative tumor spill, type I PPB is often treated with adjuvant chemotherapy [13,17]. Type II and III PPB require intensive chemotherapy and surgical resection. Radiation therapy may be used in case of non-radical resection and for PPB recurrence or metastases. PPB is strongly associated with DICER1 syndrome (OMIM * 606241), a tumor predisposition syndrome caused by constitutional pathogenic *DICER1* variants [18]. Pathogenic germline *DICER1* variants are found in nearly 70% of children with PPB, most often in combination with a somatic *DICER1* missense variant in the RNase IIIb domain (i.e. second hit mutation) [13]. Individuals with PPB who do not carry a germline *DICER1* pathogenic variant often have two somatic pathogenic variants in *DICER1* [19]. Besides PPB, several other benign and malignant tumors have been associated with *DICER1* germline variants, including multinodular goiter, thyroid cancer, ovarian sex-cord stromal tumors, cystic nephroma, nasal chondromesenchymal hamartoma, ciliary body medulloepithelioma, primary brain tumors, and sarcomas of various sites [20–26]. Surveillance for early detection of DICER1-associated tumors in patients with DICER1 syndrome has been recommended [27,28].

Differentiation between CPAM and PPB on imaging and pathology can be challenging. Studies have shown that the sensitivity of preoperative chest computed tomography (CT) for distinguishing cystic PPB from benign congenital lung lesions is low [29–31]. On pathologic evaluation it may be difficult to classify a cystic pulmonary lesion because of the wide range of morphologic features in CPAM and PPB, the possibility of mixed features within one lesion, the lack of a pathognomonic molecular marker for PPB, and the inconsistent use of definitions/classifications [13,32–34]. To ensure appropriate treatment, surveillance for early detection of second neoplasms, and genetic counseling of family members, it is imperative to differentiate CPAM from PPB. Because PPB is strongly associated with *DICER1* gene variants, *DICER1* genetic testing may be helpful in the differentiation of congenital cystic lung lesions.

This diagnostic challenge is nicely illustrated by a case in our hospital of a 10-month-old child who presented with a chronic cough. Chest X-ray and CT showed a large cystic lesion in the right hemithorax, subsequently shown to be most likely a bronchogenic cyst on histological exam after resection. Fifteen years later a sibling of the child was diagnosed with multinodular goiter and DICER1 syndrome. Germline genetic testing was subsequently performed in the child, revealing the presence of the identical pathogenic *DICER* variant that was identified in the sibling. Based on this new information, histology of the resected cystic lung lesion was reviewed, and the diagnosis was revised to PPB type I.

This case raised the question whether we have missed pathogenic *DICER1* variants in other children previously diagnosed with benign lung cysts. In the Amsterdam University Medical Center in the Netherlands, it has been standard practice to resect cystic lung lesions suggestive of CPAM but, *DICER1* mutation status was not routinely checked for. With the availability of this unique cohort, we therefore set out to review the clinical and radiographic features of all consecutive cases and performed *DICER1* sequencing in preserved lesional tissue. This cohort of unselected, consecutive patients gives information on the *DICER1* mutation status in children previously diagnosed with CPAM.

2. Methods

We performed a retrospective cohort study including all consecutive children (age 0–18 years) with a surgically removed CPAM between January 1st 2007 and December 31st 2017 at the Amsterdam University Medical Center in the Netherlands. Patients were identified by searching both our institutional pediatric surgery database and pathology database. Patients were included if the resected lung lesion was reported as a CPAM/CCAM in the pathology report. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies [35]. The Medical Ethical Committee of the Amsterdam UMC (Amsterdam, the Netherlands) stated that the Medical Research Involving Human Subjects Act (WMO) does not apply and official approval of this study by the committee was not required (W18_214#18.257 17-07-2018). CPAM tissue samples were primarily analyzed anonymously for *DICER1* variants. Variants were classified according to the American College of Medical Genetics and Genomics standards [36]. In case pathogenic *DICER1* variants were identified in lung tissue of one or more patients, all patients included in the cohort had to be informed and offered *DICER1* germline genetic testing subsequently.

2.1. Clinical features

Medical records were reviewed for clinical data including timing of initial detection (prenatal or postnatal), presence of symptoms, age at (postnatal) CT scan, and age at resection. In addition, radiology reports from (postnatal) CT scans performed during work-up of prenatally diagnosed lesions or at initial presentation for postnatally diagnosed lesions were reviewed. Available CT scans were re-assed by two pediatric radiologists. The following parameters were scored: lobar location of lesion, presence of more than one lesion, presence of a systemic vascular supply, solid appearance of lesion, hybrid appearance of lesion, and suggested subtype of CPAM (type 0–4). Pathology reports were reviewed for final pathologic diagnosis.

2.2. DICER1 gene sequencing and MLPA

Sequencing of all exons (1–28) of the *DICER1* gene was performed on DNA extracted from sections of formalin-fixed paraffin-embedded CPAM tissue samples. For our purpose, the exons, flanking intronic and untranslated regions of *DICER1* were targeted using a custom Ion AmpliSeq panel (Thermo Fisher Scientific, USA; Supplementary Table S3). In addition, primers to detect single nucleotide polymorphisms (SNPs) located in the *DICER1* gene, and 300 kb, 600 kb, and 900 kb upstream and downstream from the *DICER1* gene were included to enable detection of allelic imbalance indicative of loss-of-heterozygosity. Libraries were quantified using the Qubit 3.0 Fluorometer. DNA libraries were sequenced on an Ion 530 chip in the IonGeneStudio S5 System (Thermo Fisher Scientific). The target sequencing depth was 1,500x per amplicon. Sequences were analyzed using SeqNext software v4.1.2 (JSI Medical Systems GmbH, Ettenheim, Germany). For variant calling a variant allele fraction (VAF) cut-off value of 5% was used. DNA copy number of the DICER1 gene was measured by Multiplex ligation-dependent probe amplification (MLPA, probemix Dicer P482, MRC Holland, Amsterdam, the Netherlands).

3. Results

A total of 28 consecutive patients with CPAM, 16 girls and 12 boys, were identified. Clinical features are shown in Table 1. The pulmonary lesions were most frequently located in the left lower lobe (n = 12) and right lower lobe (n = 12). Two patients had CPAM lesions in two lobes, but no bilateral lesions were detected. In 86% (24/28) the CPAM was suspected antenatally. The age at chest CT- or MRI-scan performed during work-up of prenatally diagnosed lesions ranged from 0 months to 10 months, and the median age was 3 months. The median age at resection was 11 months (range 5–32 months). In four patients, the CPAM was diagnosed only after they had presented with symptoms attributed to their lung lesion, such as difficulty with breathing, fever, and coughing. Three out of these four symptomatic patients were older than 12 years at time of diagnosis. In this postnatally diagnosed patient group the median time between initial presentation and resection ranged from 2 to 11 months.

In 27/28 patients the CPAM subtype was reported at pathology assessment. CPAM type 1 and type 2 were the most common subtypes (n = 12 and n = 13, respectively). Pathology reports of two patients expressed some diagnostic uncertainty ('features that could be compatible with CPAM'). In five patients the resected lung tissue showed signs of inflammation. Additional pathologic diagnoses were reported in six patients, including one patient with an endobronchial typical carcinoid and five patients with pulmonary sequestrations.

3.1. Radiology reassessment

For 21 patients a CT scan was available for reassessment by two pediatric radiologists. Radiologic reassessment data are presented in Supplementary Table S4. In four patients there was evidence of a systemic vascular supply in combination with a hybrid lesion. In 9 patients (9/21, 43%) the CPAM subtype scored by the radiologists did not correspond with the subtype given at pathology assessment. The most common discordance between the presumptive radiological and final pathological CPAM subtype was found for lesions classified as CPAM type 3. Five lesions that were scored as CPAM type 3 based

Table 1
Clinical data of 28 patients with CPAM.

Case no.	Sex	Type of pre-operative imaging	Age at imaging (months)	Age at resection (months)	Affected lobe(s)	CPAM type (preoperative CT-scan)	CPAM type (pathology)
			Antenatal detection				
1	F	CT chest	2	12	LLL	CPAM2	CPAM1
2	F	MRI chest	1	5	RML	NA	CPAM1
3	M	CT chest	8	12	RLL	NA	CPAM1
4	F	CT chest	0	32	RUL	CPAM3	CPAM1
5	M	CT chest	5	9	LLL	CPAM3	CPAM1
6	M	CT chest	5	13	RLL	CPAM1	CPAM1
7	F	CT chest	3	8	RLL	CPAM1	CPAM1
8	M	CT chest	2	10	LLL	CPAM2	CPAM1
9	M	CT chest	3	11	LLL	NA	CPAM1
10	F	CT chest	10	14	RLL	CPAM2	CPAM2
11	F	CT chest	7	18	RLL	NA	CPAM2
12	M	CT chest	4	10	LLL	CPAM2	CPAM2
13	F	CTA chest	1	6	RLL	CPAM1	CPAM2
14	M	CT chest	2	9	LLL	CPAM2	CPAM2
15	F	CT chest	9	12	LLL	CPAM2	CPAM2
16	F	CT chest	4	7	RLL	CPAM2	CPAM2
17	F	CT chest	4	11	LLL	CPAM3	CPAM2
18	M	CT chest	2	12	LLL	NA	CPAM2
19	M	CT chest	1	9	RML + RLL	CPAM2	CPAM2
20	F	CT chest	4	8	RLL	CPAM1	CPAM4
21	M	CT chest	3	11	RUL	CPAM2	NA
22	F	CT chest	3	9	RUL	CPAM2	CPAM2
23	F	CT chest	2	15	LLL + LUL	CPAM3	CPAM1
24	M	CT chest	3	6	LLL	CPAM3	CPAM1,2
			Postnatal detection				
25	F	CT chest	156	161	LLL	NA	CPAM1
26	F	CT chest	7	19	RLL	CPAM2	CPAM2
27	F	CT chest	181	186	RLL	CPAM2	CPAM2
28	M	CT chest	196	199	RLL	NA	CPAM1

CPAM, congenital pulmonary airway malformation, CT, computed tomography, LLL, left lower lobe, MRI, magnetic resonance imaging, RML, right middle lobe, NA, not applicable, RLL, right lower lobe, RUL, right upper lobe, CTA CT angiography, LUL, left upper lobe.

on their solid appearance on imaging were ultimately classified as CPAM type 1 or 2 by pathology assessment. One patient in our cohort was diagnosed with a CPAM type 4 on pathologic evaluation. This lesion was scored as CPAM type 1 by the radiologists.

3.2. DICER1 gene analyses

By NGS, no pathogenic variants were detected in exons 1–28 of the *DICER1* gene in DNA extracted from CPAM tissue in 28 patients. In one patient a heterozygous *DICER1* gene variant of unknown significance was identified (c.1094C>T, p.Pro365Leu).

4. Discussion

This single-center study assessed the somatic *DICER1* mutation status in an unselected, consecutive cohort of children previously diagnosed with CPAM. We hypothesized that some previously diagnosed benign cystic lung lesions are *DICER1*-associated PPBs, a diagnosis with important clinical implications for patients and their families. However, no pathogenic *DICER1* variants were identified in our cohort.

Studies over the past years have reported conflicting evidence on the association between CPAM and PPB. Several reports describe patients who were initially diagnosed with pulmonary cystic lesions, such as CPAM, and later developed PPB [37]. Brcic and colleagues speculated that CPAM can progress to cystic PPB by acquiring a somatic pathogenic variant in *DICER1* [38]. In contrast, others argue that it is unlikely that PPB type I is the result of transformation of preexisting CPAM given the general young age at PPB diagnosis [30]. Dehner and colleagues argued that CPAM type 4 and cystic type PPB are the same clinical and pathological entity [39]. *DICER1* genetic testing has been recommended for delineating CPAM from PPB, but *DICER1* mutation status has not been well studied in those with benign pathology [30,40]. To our best knowledge, this study is the first that systematically assessed the *DICER1* mutation status in CPAM.

Because no pathogenic *DICER1* variants were identified in our cohort, the initial diagnoses of CPAM may have been correct. If CPAM type 1 and type 2 are not associated with DICER1 syndrome, questions remain regarding the pathogenesis and malignant potential of CPAM. The pathophysiology of CPAM is multifactorial and complex [7]. Several molecular mechanisms have been explored as potential contributors, but the exact etiology is not yet completely understood [9,41]. Besides PPB, other malignancies have been associated with CPAM including mucinous adenocarcinoma. CPAM type 1 frequently contains clusters of mucinous cell proliferation with oncogenic *KRAS* mutations [42]. Although cases of mucinous adenocarcinoma arising in CPAM have been reported in literature, lesions of mucinous cell proliferation in CPAM rarely progress or metastasize [42,43]. Additional molecular alterations, such as GNAS mutations, may be needed for progression to malignancy. To decide on best management of patients with CPAM, future studies on the exact pathogenesis and malignant potential of CPAM are needed.

Another important finding of our study is that CPAM subtype distinction on CT-imaging is unreliable. Classification of congenital lung lesions is important as it may influence decisions on operative management. A possible explanation for the low diagnostic accuracy of imaging is that the classification of CPAM is originally based on pathological characteristics [3]. Hermelijn et al.have argued that radiological appearance of congenital lung lesions should not be categorized using a pathology based classification as imaging features can overlap between and within various abnormalities [44]. They have developed a structured radiology report which can be used as guide for uniform reporting of congenital lung lesions and may improve the diagnostic accuracy of CT-imaging.

4.1. Limitations

Although we report the first consecutive series of *DICER1* mutation testing in benign cystic lung lesions, there are a few important limitations to this study. Firstly, one can, in spite of NGS, SNP analysis and MLPA of all *DICER1* exons, never fully exclude cryptic *DICER1* deletions. Secondly, due to the retrospective nature of the study some clinical details were missing in the electronic medical records, and for seven patients we were not able to reassess the chest CT. Finally, as is inherent to research on rare diseases, our relatively low number of CPAM lesion evaluated may have resulted in a lack of power to detect a DICER1-associated PPB (Supplementary Table S5). Larger studies are needed to draw conclusions on *DICER1* genetic testing in children with CPAM. In addition, we recommend somatic testing for more genes, such as *KRAS* and *GNAS*, to get insight into the exact pathogenesis and malignant potential of CPAM.

5. Conclusion

Our findings suggest that the initial diagnoses of CPAM were correct. Although we did not identify somatic pathogenic variants in *DICER1* in our consecutive cohort of 28 patients with CPAM, these findings should be validated through larger studies to draw conclusions regarding whether systematic *DICER1* genetic testing is required in children with a pathological confirmed diagnosis of CPAM or not.

Previous communication

NA.

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Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2023.10.031.

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