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EDITORIAL

How to become a leader in the medical profession

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We are often asked by medical students and physicians-in-training *'How can I be successful in achieving success in the clinical and/or academic medical profession'.* In particular, some are motivated solely by economic interests, others in acquiring greater leadership, and still others with the preferable incentive of being well-paid and well-respected leaders in their future chosen field of medical expertise!

To achieve success and leadership in the medical field, particularly focusing on both clinical and academic aspects, as well as economic growth, we can summarize our response with one sentence: 'Believe in your project from the bottom of your heart to achieve your ultimate high-quality results'. The statement underscores the significance of having a deep and genuine conviction in the work or project you are pursuing. When you truly believe in what you are doing, it tends to reflect in the quality of your efforts and the success of its outcomes. Here is a breakdown of its meaning:

A belief in your project: to achieve the best results, it is essential to have unwavering faith in the value and purpose of your project. This belief fuels your motivation, persistence, and commitment to achieving excellence.

From the bottom of your heart: this phrase emphasizes the importance of sincere and genuine belief and the importance of integrity. It is not just superficial or fleeting confidence but a genuinely deeply rooted conviction that comes from your innermost feelings and understanding.

Achieving high-quality results: when your belief is genuine, and not solely tempered by economic gain, it positively impacts the quality of your life's work. You will be more likely to invest time, effort, and attention to detail, resulting in outcomes that stand out for their excellence.

In essence, this advice suggests that when you believe in your project with heartfelt conviction, you are more likely to pour your best efforts into it, leading to positive outcomes that are marked by their exceptional quality and impact.

We would also offer the following specific 10 recommendations and advice for motivated and aspiring medical students and physicians-in-training:

1. **Continuous learning**: always prioritize studying and staying updated with the latest biological, clinical, and methodological knowledge.
2. **Passion and ethics**: dedicate yourself passionately to your work, while upholding ethical principles in your interactions with patients and colleagues, always marked with respect for others.
3. **Vision and dreams**: cultivate a visionary mindset that allows you to imagine and develop innovative projects aligned with your dreams.
4. **Mentorship**: seek out mentors who excel not only in their scientific expertise but also as ethical and life role models.

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5. **Collaborative environment**: surround yourself with a dynamic and enthusiastic team that fosters knowledge exchange, competition, and collaboration.
6. **Self-promotion and management**: learn to effectively market your skills and reputation, increasing your visibility while also developing leadership and management abilities.
7. **Anticipate trends**: stay ahead by anticipating and implementing the latest developments in biology, epidemiology, or clinical practice.
8. **Align with passion**: choose your specialization based on your innate talents and interests, as genuine passion contributes to higher achievements.
9. **Opportunities and networking**: while dedication and competence are crucial, seize luck, special opportunities, influential connections, and relationships to propel your success.
10. **Personal agency**: while external factors can influence your journey, ultimately, you have the power to shape your own destiny and forge your own path.

As the Roman poet Sallustio wisely advises, which he attributes to Appio Claudio Cieci, *'Faber est suae quisque fortunae'* or 'Every individual is the architect of their own destiny'.

This axiom emphasizes the idea that individuals have the power to shape and control their own lives and outcomes through their actions, decisions, and efforts. It encourages self-reliance, personal responsibility, and the recognition that one's destiny is not solely determined by external forces but is influenced by the choices they make and the actions they take.

In summary, success and leadership in the medical field require a combination of continuous learning, dedication, ethical conduct, visionary thinking, effective collaboration, self-promotion, and seizing opportunities. By embracing these principles, aspiring medical professionals can build fulfilling careers that encompass both clinical excellence and leadership prowess.

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RESEARCH ARTICLE

Rate and predictors of quantity not sufficient of sweat for chloridrometry in very young infants

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ABSTRACT

The Cystic Fibrosis Foundation (CFF) defines a quantity not sufficient (QNS) of sweat as a sample weighting lower than 75 mg, whose rate should be lower than 10% for infants younger than three months. This study aimed to verify the rate and factors associated with QNS for chloridrometry among very young babies from a low-prevalence resource-limited setting.

We recruited prospectively and consecutively newborns and young infants younger than three months undergoing coulometry assays after two abnormal immunoreactive trypsinogen results. Explanatory variables were gender, gestational age (<37 or >37 weeks), birth weight (<2.500 g or >2.500 g), weight on the day of sweat collection (<2.500 g or >2.500 g), age upon the sweat test (<43 or >43 days), daily weight gain from birth to the day of sweat collection (<25 or >25 g/day). Statistics included frequency distribution and univariate and multivariate logistic regression analyses.

One thousand sixteen individuals were included. Mean and median ages were 48 days (SD 19.4) and 43 days (range 15-90 days), respectively, and 50.7% were girls. The rate of QNS was 3.3%. Preterm (OR = 3.7), with weight on the day of sweat collection under 2.500 g (OR = 7.1) and lower daily weight gain (OR = 10.1), were more likely to produce insufficient sweat amounts.

QNS rate for chloridrometry fulfilled CFF standards in the studied population. Ideally, in the case of QNS, sweat testing should be postponed as early as possible when the infant attains more than 37 weeks (corrected age), 2.500 g on the day of sweat collection, and an optimal daily weight gain.

HIGHLIGHTS BOX

What is already known about this topic? Insufficient amount of sweat should be lower than 5% and 10% in infants older and younger than three months undergone sweat testing; weight lower than 2000-3000 g, and prematurity are predictors of insufficient sweat samples. **What does this article add to our knowledge?** Collection of a sufficient amount of sweat is feasible in resource-limited settings; daily weight gain from birth to the date of sweat collection is an additional non-negligible predictor for a lower amount of sweat. **How does this study impact current management guidelines?** In resource-limited settings, QNS rates could fulfill international standards among infants by postponing sweat testing when they attain 37 weeks of gestational age, weight gain of 25 g/day, and 2500 g on the day of sweat collection.

KEY WORDS
Sweat test; quantity-not-sufficient; newborns; infants.

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INTRODUCTION

Detection of elevated values of sweat Cl− by the quantitative pilocarpine iontophoresis test (QPIT) performed via chloridometer is accepted as the gold standard in CF diagnosis. This well-known technique is performed in three stages, as follows, cholinergic stimulation of sweating with iontophoresis, collection of the sweat sample, and measurement of sweat Cl− concentration (1).

Infants must produce enough sweat (*i.e.*, over 75 mg) when undergoing sweat testing. Otherwise, a new collection must be performed (2-4). It is well known that young infants may produce insufficient (QNS) sweat, especially those younger than three months and low-weight for age individuals. Then, to minimize an unsuccessful rate, the Cystic Fibrosis Foundation (CFF) suggests waiting until the children are at least two weeks of age and of weight 2 kg (5).

The CFF accepts a QNS rate lower than 5% and 10% in infants older and younger than three months of age, respectively (3, 6, 7). Moreover, sweat volumes lower than 75 mg collected over 30 minutes should not be analyzed because electrolyte concentration decreases with lower sweat weight, increasing the risk of evaporation and, consequently, unreliable results (8). Specialized laboratory and skilled technicians can reduce QNS rates (7).

To our knowledge, no study on this subject has been carried out in low prevalence low-middle income countries. On the other hand, single-centered works conducted in high-income ones enrolled a total of 1,057 subjects and found a QNS rate ranging from 12 to 26% (9-11). Furthermore, African American ethnicity, weight lower than 2-3 kg, and prematurity have been reported as the main predictors of insufficient sweat samples (9-11). Therefore, this study aimed to verify the rate and factors related to QNS for chloridrometry in Brazilian newborns and infants younger than three months.

MATERIALS AND METHODS

Study design, population, and setting

This study recruited prospectively 1,016 clinically stable newborns and young infants aged less than three months. They had two previous positive (*i.e.*, >70mg/L) immunoreactive trypsinogen (IRT) results and, after pilocarpine iontophoresis, underwent chloridrometry assay (1). Our Statewide IRT-IRT based NBS program was implemented in the early 2000's is mandatory for all stillborn, and due to financial constraints genotyping did not take part in our NBS protocol. The program coverage was about 90-95% during the study period. The median age of the patients was five days old at the first IRT and 15 days of life for those in which the first dosage was higher than 70 mg/L. There were no relevant delays in the age of the participants at the time of the first and second IRT.

Sweat testing was exclusively performed at the Reference Center for Newborn Screening and Genetic Diagnosis, located in Belo Horizonte, the capital of Minas Gerais State, Southeastern Brazil, where the average CF incidence is about around 1:11.000.

Figure 1 depicts the borders of Minas Gerais State and its neighboring Brazilian States showing the location of Belo Horizonte city and some of the main Brazilian cities. Its population has about 20 million inhabitants, distributed in 853 municipalities, and a surface area equivalent to France.

Assessing QNS in a single center ensures homogeneity in sweat collection. We excluded subjects older than 90 days of life, with skin lesions (such as atopic dermatitis and eczema), any clinical instability (*e.g.*, previous *meconium ileus*, exacerbation, dehydration, hyponatremia, no acute illnesses) (1), insufficient sweat quantity, as well as those with intermediate results for coulometry upon the day of sweat collection.

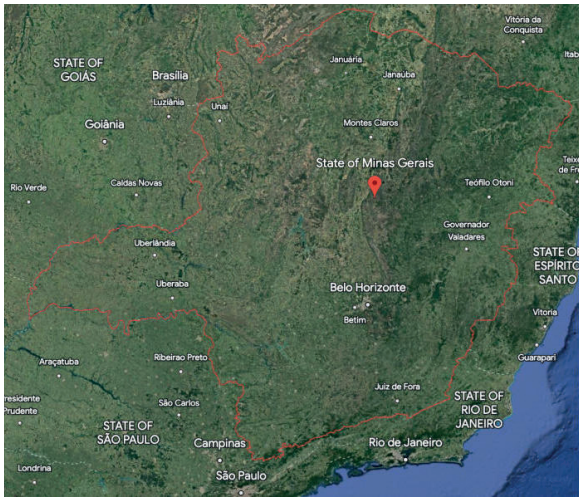

***Figure 1**. A map of the State of Minas Gerais shows the neighboring states. Source: Google Earth.*

Sweat sample collection

Sweat samples were collected in the left or right forearm through the standard Gibson and Cooke technique, followed by chloride titration (11). According to well-established guidelines, the minimum sample weight of 75 mg was pre-defined to consider a sufficient amount of sweat (1, 5, 8, 9).

Statistics

Categorical variables were presented through frequency and percentages, as follows, gender, gestational age (<37 or >37 weeks), birth weight (<2.500 g or >2.500 g), weight at the day of sweat collection (< 2.500 g or > 2.500 g), age upon the sweat collection (<43 or >43 days of life), and daily weight gain from birth to the day of sweat collection (<25 or >25 g/day). Analysis corresponded to the day of sweat collection (one single sample per individual) and included descriptive statistics, univariate and backward stepwise multivariate logistic regression; the latter was used to identify independent predictors of QNS whose p-value <0.20 in the univariate step. Hosmer and Lemeshow's goodness-of-fit test was applied to keep the explanatory variables in the final model and evaluate the final model's adequacy. The significant level was p .05. Analyses were performed through SPSS software, version 23 (SPSS Inc., Chicago, Illinois).

RESULTS

A total of 1,016 newborns and infants were enrolled. **Table 1** displays the general characteristics of the subjects studied.

There was a slight predominance of girls and those with daily weight gain higher than 25 g. Most subjects were born after the 37th week of gestational age, had an appropriate weight for birth, and had no CF. The mean and median age were 48 days (SD 19.4), and 43 days (range 15-90 days), respectively. Of all, 51.5% had less than 43 days of life upon sweat collection, and 150 (14.7%) were newborns. Notably, the observed overall QNS rate was as lower as 3.3% with a 95% CI of 2.3% to 4.6%, revealing excellent statistical precision.

Among the 19 confirmed CF cases, the proportion of girls, gestational age ≥37 weeks, and birth weight ≥2.500 were 52.6%, 94.7%, and 89.4%, respectively. There were no false-positive coulometry tests; all of them presented typical clinical features of CF.

Table 2 shows the univariate analysis of subjects with and without sufficient sweat samples.

One hundred and fifty-four out of 1,016 were preterm babies, but just 21 (13.6%) had QNS sweat samples; conversely, for full-term infants, this rate was still lower (1.5%, 13 out of 862). Almost 80% of infants with QNS results had a low daily gain (under 25 g per day), and 58.8% were girls.

Five hundred twenty-three infants under 43 days were enrolled, but as few as 18 (3.4%) had QNS. The youngest patient had 15 days of life and 150 newborns, *i.e.*, 14.7% of infants were younger than 29 days of life. Only three of them (2%) had insufficient sweat amount.

As shown, gestational age, birth weight, weight on the day of sweat collection, and daily weight gain, whose p-values were lower than 0.20, became the candidates' explanatory variables that should be included in the multivariate analysis.

***Table 1**. Descriptive characteristics of the 1,016 studied subjects.*

	N	%
Gender		
Girls	515	50.7
Boys	496	48.8
Not recorded	5	0.5
Gestational age (weeks)		
<37	154	15.2
>37	862	84.8
Birth weight (g)		
<2.500	187	18.4
>2.500	822	80.9
Not recorded	7	0.7
Weight at the day of sweat testing (g)		
<2.500	29	2.9
>2.500	950	93.5
Not recorded	37	3.6
Age at the time of sweat collection (days of life)		
<43	523	51.5
>43	493	48.5
Daily weight gain from birth to the day of sweat testing (g)		
<25	431	42.4
>25	543	53.4
Not recorded	42	4.1
CF diagnosis		
Yes	19	1.9
No	957	94.2
Not recorded	40	3.9
Insuficient sweat sample Yes	34	3.3

Table 2. *Characteristics of infants with and without sufficient sweat weight.*

	Insufficient sweat weight		Sufficient sweat weight		p-value
	N	%	N	%	
Gender					0.35
Girls	20	58.8	495	50.4	
Boys	14	41.2	482	49.1	
Not recorded			5	0.5	
Gestational age (weeks)					< 0.01 *
<37	21	61.8	133	13.5	
≥37	13	38.2	849	86.5	
Birth weigh (g)					< 0.01 *
<2.500	19	55.9	168	17.1	
≥2.500	13	38.2	809	82.4	
Not recorded	2	5.9	5	0.5	
Weight at the day of sweat collection (g)					< 0.01 *
<2.500	11	32.4	18	1.8	
≥2.500	18	52.9	932	94.9	
Not recorded	5	14.7	32	3.3	
Daily weight gain from birth to the day of sweat collection (g/day)					< 0.01 *
<25	27	79.4	404	41.1	
≥25	2	5.9	541	55.1	
Not recorded	5	14.7	37	3.8	
Age at the time of sweat collection (days)					0.86
<43	18	52.9	505	51.4	
>43	16	47.1	477	48.6	

* Statistically significant.

Table 3 depicts the final multivariate model. Among the variables previously selected from univariate analysis, only gestational age lower than 37 weeks, weight on the day of sweat collection under 2.500 g, and daily weight gain lower than 25 g remain independent predictors of QNS in our population. Results obtained for Hosmer and Lemeshow's test ($p = 0.845$, $R^2 = 0.291$) indicate the appropriateness of the final model.

Table 3. *Predictors of QNS rates among 1,016 newborns and young infants.*

	OR	95% CI	P-value
Gestational age (weeks) <37	3.7	1.5-9.1	0.005 *
Weight at the day of sweat collection (g) <2.500	7.1	2.6-19.6	<0.001 *
Daily weight gain (g) <25	10.1	2.3-44.4	0.002 *

* Statistically significant.

DISCUSSION

To our knowledge this is the first study conducted in a single center of a resource-limited, low-prevalence setting that simultaneously assessed the QNS rate and its predictors exclusively in 1,016 infants younger than three months, the target age group of CF newborn screening. We found that the overall QNS rate was 3.3%, and that rate was independently associated with daily weight gain lower than 25 g (OR = 10.1), low weight on the day of sweat collection (OR = 7.1), and prematurity (OR = 3.7). We did not find a relationship between age at the time of sweat collection, *i.e.*, before or after 43 days of life (in other words, before or after six weeks) and QNS.

The results of this study have similarities and differences with related works published so far; we discuss below the weaknesses and strengths related to these issues.

Factors such as age at the time of sweat collection, technical procedures, and QNS definition may contribute to those differences (2). Some studies reported QNS rates without its predictors, and others found this relationship but did not perform multivariate analysis (10, 11). Moreover, published studies had a retrospective design (2, 9) and a smaller sample size (between 118 and 742 infants) than ours (2, 9-11). Our preterm babies have an OR of 3.7 for QNS, an intermediate estimate between the results obtained (from 2.4 to 19.0) in two other studies (2, 9). Another non-negligible discrepancy was our success rate (around 97%). For instance, enrolling the same age group (infants younger than three months), three American teams reported QNS rates from 12% to 26% (9-11). We also found that preterm and full-term infants had different QNS rates, *i.e.*, 13.6% and 1.5%, respectively. This finding has already been reported but with higher ranging rates, *i.e.*, 46.2% to 49% for preterm infants and 8% to 16% for full-term infants (2, 10). In addition, as an original contribution not previously assessed, we also found that a daily weight gains lower than 25 g strongly (OR = 10.1) predicts QNS.

QNS rate increases as the weight at the sweat collection decreases. We found a QNS rate of 25% in infants under 2.000 g (data not shown). A similar finding was demonstrated in other studies that found a QNS rate of 77.8% and 31.2% for infants under 2.000 g and between 2.000 and 3.000 g at the time of sweat collection, respectively (9). Kleyn and coworkers reported that the chance of QNS results decreases by 70% for every 1.000g of weight gain after birth (2). It is well known that birth weight under 2,500g is related to a QNS (2). However, we recruited 187 infants with low birth weight, and only 19 (10.2%) had QNS results (see **Table 2**), lower than those described in the literature.

Therefore, it is worth noting that despite methodological differences, except for daily weight gain, the original contribution of our study, the results from this study point in the same direction as those obtained in high-income countries.

Age on the day of the sweat collection is another critical issue to discuss, because there is no consensus on the relationship between QNS and the best age to perform sweat testing. Although most studies describe a direct relationship between QNS and lower age on the day of the sweat collection (2, 11, 13), some authors questioned whether age at sweat sample collection is one of the predictors of QNS (3, 5). However, only 2% of our 150 newborns had QNS results (data not shown).

An additional comment of this study is related to the generalizability of the obtained results. Due to their population-based characteristic, they only apply to the under-three-month-old children's participants of the State of Minas Gerais NBS program (see **Figure 1**) and could not apply to the same age group of subjects screened in the other Brazilian States.

Lastly, we should pinpoint that the more risk factors the child has, the more the QNS rate increases, getting around a chance of 86% for those prematurely born and with a body weight under 3000 g (10).

CONCLUSIONS

Along with previously mentioned studies, sweat collection in newborns and young infants is entirely feasible. Therefore, sweat testing should not be delayed in infants with a positive CF NBS test because appropriate collection procedures can minimize failed tests, reduce costs and parents' anxiety, and benefits the health system (12).

Our results suggest that QNS rates for chloridrometry could fulfill CFF standards in newborns and young infants from resource-limited, low prevalence settings. However, in cases of QNS, sweat testing should be postponed as early as possible when the infant attains more than 37 weeks (corrected age), 2.500 g on the day of sweat collection, and an optimal daily weight gain.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The funding institutions played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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Author contributions

RMB contributed to the manuscript conception, writing, revision, and editing. CGA contributed to the manuscript conception, writing, editing and critical revision of the manuscript. OGS contributed to data collection, interpretation, and analysis. DN supervised and/or performed SC assays. PC conceived the study, and the study design; investigation, methodology, funding acquisition, project administration, resources, validation; manuscript conception, writing, editing and to critical revision of the manuscript.

Ethical approval

Human studies and subjects

All relevant ethical guidelines have been followed for data collection and reporting. The research protocol was approved by the Research Ethics Committee of Federal University of Minas Gerais, under number CAAE 21958014.1.0000.5149 and in compliance with the Declaration of Helsinki.

Animal studies

N/A.

Data sharing and data accessibility

Data are available on reasonable request. All data relevant to the study are included in the article. Additional individual patient data are available in the deidentified format on request to the Corresponding Author.

Publication ethics

Plagiarism

The contents of the article are original and any overlaps with other articles are by the Authors themselves and appropriately cited.

Data falsification and fabrication

All the data correspond to the real.

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REVIEW

Diagnosis of congenital airway abnormalities in children

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ABSTRACT

Congenital lung lesions are relatively rare but are an important consideration in any child with lung disease especially if the disease is recurrent or not resolving. Some of these lesions cause severe symptoms shortly after birth while others may not present with symptoms for years. Antenatal ultrasound has made it possible to diagnose some of these lung lesions early, which were not possible to diagnose in the past.

Most congenital airway lesions are not diagnosed antenatally especially if they are not associated with cardiac lesions. Not every mother has an antenatal ultrasound in the developing world, which leads to late diagnosis of many congenital lesions with significant consequences.

There is a large number of different types of congenital airway abnormalities, but can be divided in structural abnormal airway, external compression and airway fistula. Long segment congenital tracheal stenosis presents early especially if associated with left pulmonary sling.

It is important that airway lesions are diagnosed early to determine the correct diagnosis and management. Plain chest X-ray may be very indicative of airway pathology, and these should be evaluated to determine if the airways are visible, to determine narrowing, displacement or abnormal branching.

The diagnosis and management of children with airway pathology needs a team approach with skills needed in airway management, imaging, cardiology, bronchoscopy and airway surgery.

IMPACT STATEMENT: Congenital lesions are rare, but if undiagnosed, they may have significant consequences. These lesions are associated with abnormalities including congenital heart disease, which will complicate their diagnosis and management, particularly congenital airway malformations. Bronchoscopy plays an important role in diagnosis, intra-operative and post-operative management. Interventional bronchoscopy is useful in treating congenital airway abnormalities.

KEY WORDS
Congenital airway abnormalities; bronchoscopy; tracheal stenosis; chest CT-scan; contrast bronchography.

INTRODUCTION

Congenital lung lesions are relatively rare but are an important consideration in any child with lung disease especially if the disease is recurrent or not resolving. Some of these lesions cause severe symptoms shortly after birth while others may not present with symptoms for years. Antenatal ultrasound has made it possible to

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diagnose some of these lung lesions early, which were not possible to diagnose in the past. However, many of these lesions will have disappeared at term.

Congenital lesions involve the airways, parenchyma, arterial tree, chest wall and the diaphragm. Sometimes these lesions are not diagnosed in childhood and present in adults as episodes of recurrent pneumonia or malignancies (1-3). In the developing world there is limited access to antenatal ultrasounds and some of these congenital lesions will only be diagnosed much later or once they have become complicated and infected (4).

WHEN TO CONSIDER A CONGENITAL LUNG LESION?

Neonatal period

A neonate with a significant lesion will present with respiratory distress. The lesions which present early are congenital cystic adenomatoid malformations (CCAM) and diaphragmatic hernias because they are space occupying (5). The rest of the ipsilateral lung may be hypoplastic.

It may be very difficult to distinguish these two lesions because both are cystic on the chest X-ray. Children with mayor airway pathology may present early. Factors that determine the time of presentation include severity of narrowing, combination of lesions and the presence of congenital heart disease. Difficult intubation and feeding issues may indicate airway pathology.

Infant and older child

The infant and child with a congenital lesion will present with recurrent pneumonia or non-resolving pneumonia that is localized to the same region of the lung (6).

During acute infection it will be difficult to identify the lesion radiographically. The lesions that present with recurrent infection are CCAM, bronchogenic cysts, duplication cysts and sequestrations.

WHY ARE CONGENITAL LUNG LESIONS IMPORTANT?

Some of these lesions have a very high mortality if not diagnosed early and treated correctly (diaphragmatic hernia, tracheal stenosis). These children are susceptible to recurrent infections that may lead to bronchiectasis. Some of these lesions are associated with other congenital abnormalities and congenital cardiac lesions.

Persistent/recurrent wheezing

Children who present with persistent wheeze, not responding to asthma treatment have a high incidence of congenital abnormalities. Congenital abnormalities have been reported in up to 45% of cases in bronchoscopy studies (7-10).

The airway narrowing is due to abnormalities of the wall of the airway or external compression of the airway. Vascular compression of the airways was observed in 13%-26% of children who underwent bronchoscopy for persistent wheezing, stridor, and apnea (11). Double aortic arch is the most common vascular abnormality, causing both tracheal and esophageal compression.

DIAGNOSIS OF AIRWAY PATHOLOGY

- Chest X-ray.
- Chest Computed Tomography (CT) scan.
- Bronchoscopy.
- Bronchograms.
- Echocardiography (ECHO).
- Contrast swallow study.
- Magnetic Resonance Images (MRI).

How does the chest X-ray help?

It is important to evaluate previous chest X-rays as that may indicate if the lesion is congenital or acquired. If the X-ray was never normal it makes the diagnosis of a congenital lesion more likely. CCAM may rarely present bilaterally, as most congenital lung lesions are unilateral. Combinations of congenital lesions do occur but are more commonly seen on the same unilateral side. It is important to determine if lesions are cystic or solid from the X-ray presentation. Solid lesions may cause more airway compression *versus* cystic lesions which can cause mediastinal shift.

Make sure that the trachea and bronchi are clearly visible on the X-ray especially in children who present with stridor and wheeze.

Some of these congenital lesions are recognizable on the chest X-ray as they are preferentially located in specific areas of the lung, *e.g*. congenital lobar emphysema (CLE) in the left upper lobe.

Clues to the presence of congenital lung anomalies include: (1) thoracic asymmetry; (2) focal mass/consolidation; (3) focal hyperlucency; (4) airway abnor-

malities; (5) vascular abnormalities; and (6) other lesions, including vertebral anomalies, gastrointestinal anomalies, and cardiac anomalies (12).

Chest X-ray: looking at the airways (Figure 1A)

The following may be indicative of airway pathology (13):

- Lack of visibility.
- Narrowing.
- Abrupt discontinuity.
- Displacement of bowing.
- Abnormal branching.
- Focal or unilateral overinflation.

CT/MRI (Figure 1B)

Both CT and MRI are used for detailed visualization of airways as well as vessels when thin slices are acquired, and an intravenous contrast agent is used. Three-dimensional (3-D) and minimum-intensity projection reconstructions can be obtained with both modalities (14). Inspiration/expiration or dynamic cine can be used for airway evaluation and to determine if malacia is present. It is helpful to evaluate the airway without an endotracheal tube (ETT) in place as the ETT can obscure the airway lesions and prevent accurate assessment of airway narrowing (13). If an ETT is in place, it should be positioned as high as possible above any stenosis (**Figure 1B**).

Contrast bronchography (Figure 1C)

Bronchography enables the assessment of the trachea and the more distal bronchi. Unlike bronchoscopy, and since it is performed in real time with the infant spontaneously breathing, the airways are assessed throughout the respiratory cycle. It is simple to perform in infants who are already intubated and is also useful in diagnosing fixed airway stenosis. Contrast bronchography is used in children with prolonged airway compression who develops secondary malacia (14).

Bronchoscopy is still necessary to identify complete tracheal rings. Examination of the airway under direct vision by the surgeon at operation has been more useful than imaging in deciding which surgical approach is most suitable for several patients.

Bronchography can be performed by injecting isotonic non-ionic contrast down the working channel of a flexible bronchoscope (**Figure 1c**) (15).

Bronchoscopy (Table 1)

Bronchoscopy has a role in the diagnosis of airway pathology, the intraoperative management, postoperative management, and long-term follow-up. To evaluate both upper and lower airways, rigid and flexible bronchoscopy should be combined. The role of bronchoscopy in both anterior and posterior aortopexy have increased during the last number of years (16, 17). During these operations bronchoscopy is used to guide the improvement of airway size and stiches are inserted under bronchoscopy vision. Persistent wheezing, stridor and difficult breathing are indications to perform bronchoscopy and may be indicative of airway pathology.

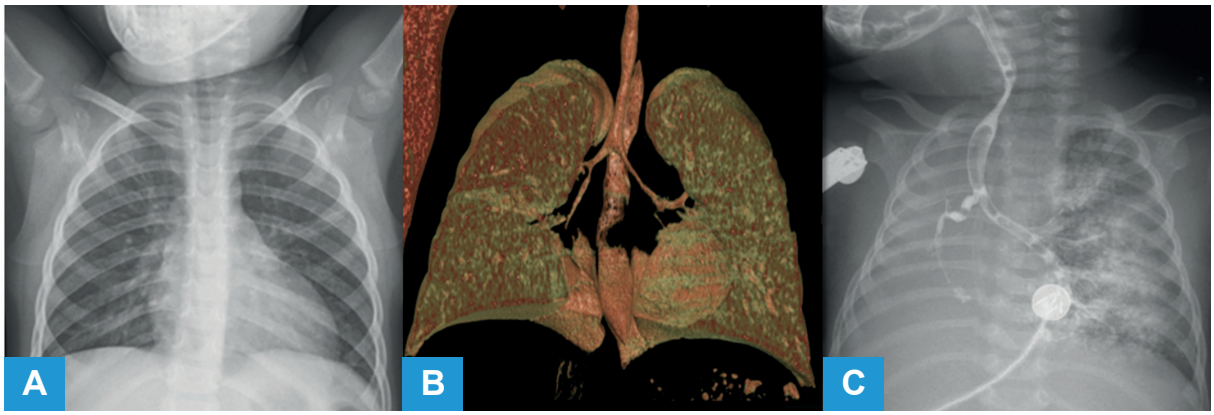

***Figure 1**. 3-year-old baby with noisy breathing: (**A**) chest X-ray demonstrates that the distal part of the trachea is not clearly visible; (**B**) CT scan reconstruction showing the tracheal stenosis but also narrow main bronchi with the right especially narrow; (**C**) tracheobronchogram done with water soluble contract medium demonstrates tracheal narrowing just below ETT. The right main bronchus is also narrow with absent RUL and RML bronchus.*

In cases of difficult intubation and ventilation, bronchoscopy is essential to exclude congenital airway pathology.

Echocardiography

Congenital airway lesions are associated with cardiac abnormalities (14). Echocardiography needs to be performed before airway surgery to plan the correct surgical procedures and cardiac lesions may have to be corrected at the same time. Long segment tracheal stenosis is associated with left pulmonary artery (LPA) sling.

Contrast study

Contrast swallow studies may be helpful in identifying different types of vascular compression (**Table 2**) (18).

Contrast swallow studies is also important in the diagnosis of laryngeal clefts, H-type tracheoesophageal fistula (TOF), swallowing incoordination and reflux. It is important to identify gastroesophageal reflux as the additional inflammation my worsen airway pathology and reduce the chance of successful surgical repair.

Table 1. *Bronchoscopy findings in congenital airway abnormalities.*

CONGENITAL AIRWAY ABNORMALITIES		BRONCHOSCOPY FINDINGS
Airway agenesis/ stenosis	Tracheal agenesis	• Confirming esophageal intubation and TOF or BOF
	Bronchial agenesis	• Absence of bronchus or rudimentary bronchus • Deviation of trachea • No carina visible • Airway narrowing due to shift of mediastinum • Compression by surrounding vessels
	Bronchial atresia	• Blinding-ending bronchus or segmental bronchus
	Hypoplastic lung	• Abnormal bronchial configuration • Absent RUL and RML
	Tracheal stenosis	• Solid tracheal rings • LPA compression • Tracheal bronchus • Abnormal position of carina
Airway branching anomalies	Tracheal bronchus	• Displaced RUL bronchus, • supplying a normal RUL about 2cm above carina • Supernumerary bronchus, existing in addition to a normal RUL bronchus • Rudimentary blind ending RUL bronchus • LUL tracheal bronchus rare
	Bridging bronchus	• Pseudocarina at lower level T5-7 • T-shape pseudocarina due to angle of BB from LMB • Anormal bronchus, originating from the LMB crosses • Airway stenosis • LMB vascular compression
	Heterotaxy syndromes	
	o *Right isomerism*	• Bilateral right-side atria • The abnormal bronchial branching patterns includes bilateral right-side bronchial branching
	o *Left isomerism*	• Bilateral left-side bronchial branching
	Scimitar syndrome	• Absent RUL bronchus
CONGENITAL AIRWAY ABNORMALITIES		**BRONCHOSCOPY FINDINGS**
Airway fistula	Laryngotracheoesophageal cleft	• Redundant posterior mucosa herniating into the laryngeal lumen • Determine type according to the level and extend of connection
	Congenital trachea-oesophageal fistula (TOF)	• Position of fistula • Commonly close to carina • Tracheomalacia • Vascular abnormalities
	Congenital broncho-oesophageal fistula (BOF)	• Fistula is usually short and is running directly from the esophagus to a main or segmental bronchus

→

Airway function abnormality	Primary ciliary dyskinesia	
External airway compression	Bronchogenic Cyst (BC)	• Compression of trachea • Prominent carina • Compression of bronchi
	Foregut duplication cyst	• Compression of trachea • Prominent carina • Compression of bronchi • Shifting of mediastinum
	Vascular compression	
	o *Double aortic arch (DAA)*	• Compression and indentation of the right wall of the right wall of the distal trachea • RMB opening can be narrowed
	o *Left pulmonary artery (LPA) sling*	• Distal tracheal compression with significant pulsations on both anterior and posterior wall • Difficult to find carina • Tracheal stenosis may be present
	o *Left main bronchus (LMB) compression*	• Narrow LMB just below carina • Pulsation both from medial and lateral • Distal to narrowing LMB is patent
	o *Innominate artery compression*	• Anterior tracheal wall compression with pulsation • Tracheomalacia • Coming from left lower to the right upper portion of trachea
	o *Interrupted aortic arch*	• Compression of the LMB
	o *Right sided aortic arch with aberrant subclavian artery*	• Tracheal compression from the right side as well as posterior
	o *Absent pulmonary valve*	• Compression of the lower trachea, LMB and RMB or bronchus intermedius
Others	Horseshoe lung	• Abnormal right bronchial branching
	Mediastinal mass causing airway compression	• Anterior or posterior compression of trachea
	Tracheobronchomalacia (TBM)	
	o *Congenital (Primary)*	• Spontaneous respiration under general anaesthesia needed to detect more than 50% bulging of the Membranous s trachea during coughing or during expiratory phase of the respiratory cycle • Widening of the posterior membranous wall with a crescent shaped lumen of the trachea. Associated TOF
	o *Acquired (Secondary)*	
	Airway compression associated with congenital heart disease	• Compression of different parts of bronchial tree. LMB compression by enlarge left atrium • PA can compress both main bronchi

Table 2. *Types of vascular compression as was identified on contrast swallow.*

Anterior tracheal, posterior esophageal indentations	double aortic arch
Normal tracheal, posterior esophageal indentation	aberrant subclavian artery
Posterior tracheal, anterior esophageal indentation	pulmonary sling
Anterior tracheal indentation, normal esophageal	Innominate arterial compression

AIRWAY AGENESIS/STENOSIS

Tracheal agenesis

Tracheal agenesis is a rare and usually a fatal malformation. Tracheal agenesis can be divided into three types: type 1, the proximal trachea is absent, and a short distal trachea is present and connected to the esophagus via a TOF; type 2 (most common), most of the trachea is absent with a short carina dividing into

right and left bronchi and usually but not always TOF and type 3, the right and left bronchi arise separately from the esophagus (19). Tracheobronchial or esophageal stenosis might be present.

Bronchial agenesis

Bronchial agenesis more commonly affects the left rather than right side and is associated with absence of the ipsilateral lung and pulmonary artery (PA) resulting in cardio-mediastinal shift to that side with overinflation of the contralateral lung.

This shift produces distortion of cardio-mediastinal structures, which is more marked when the right lung is absent because of greater shift of the normally left-side heart, associated vessels, and airways. Most cases of unilateral pulmonary agenesis are associated with other anomalies, including congenital heart disease, other vascular abnormalities, pulmonary sling, other PA anomalies, anomalous origin of arch great vessels, esophageal atresia, tracheal stenosis, lung, and vertebral anomalies (20, 21).

Bronchial atresia (Figure 2A, B)

Bronchial atresia is increasingly being reported in conjunction with congenital pulmonary airway malformation and CLE as a diagnosis depicting an abrupt interruption of the airway with a distal mucus plug (22, 23). Atresia is an abrupt complete interruption of the bronchus which can be identified on CT-imaging as a mucus plug distal from the atresia and a local hypodense region distally (12). The mucus plug is formed due to accumulated mucus produced in the patent distal bronchus (mucocele).

The hypodense region is a result of hyperinflation of the excluded lung parenchyma by collateral ventilation through the pores of Kohn.

In younger children, atresia may be difficult to diagnose due to the small diameter of distally located airways in relation to the resolution of the CT-scanner.

Hypoplastic right lung

Hypoplastic lung occurs due to a decreased number of branching generations of the airways, with decreased number of acini and alveolar size (1). Right sided hypoplasia is much more common than left sided lesions.

Tracheal stenosis

Congenital tracheal stenosis (CTS) is a rare condition with an estimated incidence of 1 in 64,500 births (24). CTS is an embryological abnormality of the tracheal skeleton, with the presence of complete tracheal rings along the stenotic segment and creating a fixed narrow tracheal lumen. CTS could be focal or present over a long segment and is usually associated with absence of the posterior trachealis muscle with complete cartilaginous rings in the affected regions.

The symptoms start in a few days after birth and symptoms are associated with the severity of the stenosis more than stenotic length. The symptoms are variable and are directly related to the degree of narrowing of the lumen and stenotic length.

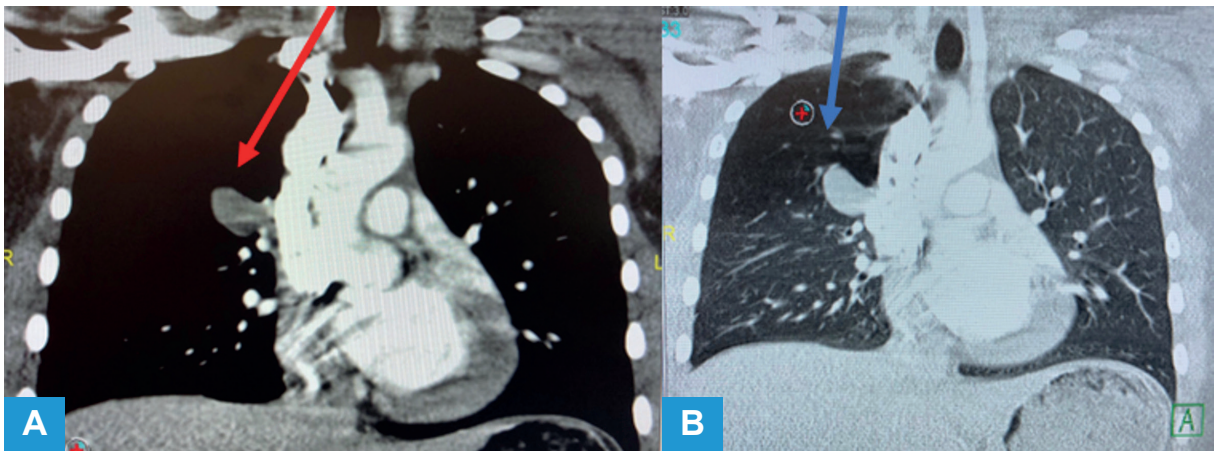

***Figure 2A, B.**. 9-year-old girl: chest CT scans demonstrate RUL bronchial atresia with mucocele and hypodense area visible in the RUL area. Lobectomy was done due to recurrent infections.*

CTS is associated with several other lesions including tracheal bronchus, other airway/lung anomalies as well as pulmonary sling, other structural cardiovascular disease, H-type TOF and Down syndrome.

Long-segment tracheal stenosis is strongly associated with type 2 pulmonary sling, occurring in 2 out of 3 cases (25). In the PA sling anomaly, the left PA arises from the right PA and courses to the left hilum between the trachea and esophagus.

There is a variety of airway abnormalities accompany the type 2 sling, including separate right upper lobe (RUL) bronchus or diverticulum at the normal carinal level resembling a tracheal bronchus, long-segment airway stenosis, low horizontal pseudocarina and bridging right bronchus arising from the left bronchus (20, 26).

In the type 1 pulmonary sling, the airway is usually not stenotic, but the right bronchus might be compressed by the sling or malacic, resulting in air trapping in the right lung. A tracheal bronchus might be present, and the carina is at the normal level (20, 27).

Congenital cardiac anomalies are often also associated with pulmonary sling (mostly type 2) including ventricular septal defect (VSD) or more complex heart disease. Lung abnormalities also occur, including hypoplastic or even absent lung (usually right), as well as bronchopulmonary malformations such as bronchogenic cyst, pulmonary sequestration, and scimitar syndrome; gastrointestinal anomalies might also be present (27).

The gold standard for the diagnosis of CTS is the rigid and flexible airway endoscopy. Sometimes the airway is so narrow that even an ultrathin flexible scope cannot be passed through the stenosis. CT or MRI are essential to study the associated vascular malformations.

The left PA is reimplanted onto the left side of the main PA. Sliding tracheoplasty is the technique of choice for long-segment tracheal stenosis, allowing for tracheal repair without the use of graft or prosthetic materials, promoting easier postoperative recovery, fewer infectious complications, and better long-term outcomes. In most of the cases, there is not a transition zone between the normal and complete rings. Only in few cases it is possible to identify a transition tracheal segment with rings from normal horseshoe shape to a complete ring (28-30).

AIRWAY BRANCHING ANOMALIES

Tracheal bronchus

There is a 13-fold increase in the incidence of tracheal bronchus in children with congenital heart disease including complex cardiac anomalies (31). Especially Down syndrome is commonly associated with a tracheal bronchus. A tracheal bronchus is almost always on the right side but is occasionally on the left or even bilateral, especially in the context of right isomerism (32).

Tracheal bronchus can be completely asymptomatic or be associated with recurrent pneumonia, stridor, and respiratory distress (21). It is a displaced bronchus supplying the whole RUL rather than a supernumerary accessory bronchus. The origin of the bronchus can be stenotic, and occasionally the anomalous branch ends blindly as a tracheal diverticulum.

Bridging bronchus (BB)

The abnormality consists of an abnormal bronchus, originating from the left main bronchus (LMB), which crosses (bridges) the mediastinum and supplies the right lower lobe (RLL), and often the right middle lobe (RML) (33). It is associated with a LPA sling, where the LPA arises from the right PA and passes posteriorly, above the right main bronchus, between the trachea and esophagus, to the hilum of the left lung (34).

Heterotaxy syndromes

Heterotaxy syndromes are associated with abnormal abdominal situs, organ anomalies, aberrant airway, and pulmonary vascular branching as well as variable simple to complex underlying cardiovascular abnormalities (35, 36).

Right isomerism

Characterized by asplenia, horizontal liver, complex heart disease and bilateral right-side atria. The abnormal bronchial branching patterns includes bilateral right-side bronchial branching (eparterial, short mainstem bronchi) and bilateral trilobed (right) lungs (13).

Left isomerism

Characterized by poly-splenia, absent intrahepatic inferior vena cava (IVC) with azygous continuation. Simple to complex cardiac anomalies along with bilateral left-side atria can be present. The abnormal bronchial branching patterns includes bilateral left-side bronchial

branching (hyparterial, long mainstem bronchi) and bilateral bi-lobed (left) lungs (21).

Scimitar syndrome

Scimitar syndrome is characterized by hypoplastic lung (almost always on the right side), aberrant airway branching and hypoplastic right pulmonary artery (RPA). Ipsilateral anomalous pulmonary vein (vertical curved scimitar vein) usually draining to the IVC, and pulmonary sequestration or anomalous systemic vessel from the upper abdominal aorta to the RLL. Right diaphragmatic eventration or hernia may be present.

The airway branching anomalies include absent RUL bronchus with only two lobar bronchi, often accompanied by an aberrant RLL bronchial branch supplying a horseshoe segment of right lung extending behind the IVC across the midline to the left side, abutting or even fused with the left lung (37, 38).

AIRWAY FISTULA

Laryngotracheoesophageal clefts (Figure 3)

They are associated with the VACTERL (vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, cardiac anomalies, renal anomalies, and limb anomalies) spectrum as well as several syndromes including CHARGE (coloboma, heart malformation, choanal atresia, mental retardation, genitourinary and ear anomalies) and DiGeorge syndromes (39). Laryngotracheobronchial malacia frequently coexists with the clefts in these children. Laryngotracheoesophageal clefts are divided into four types depending on the length and location of the defect (40). A cleft should be considered in the cases of recurrent pneumonia or suspected aspiration. The aspiration into the airway through the cleft might be seen on an esophagram but can be mistaken for pharyngeal aspiration or a TOF. A larger cleft might be recognized on CT; however, the diagnosis and extent are defined by laryngoscopy.

The Benjamin-Inglis classification system published in 1989 describes four types of laryngeal clefts: type I involves an interarytenoid defect to the level of the true vocal folds; type II, partial extension through the posterior cricoid cartilage; type III is an extension completely through the posterior cricoid cartilage and possible extension into the cervical trachea and type IV involves extension into the intrathoracic trachea (40).

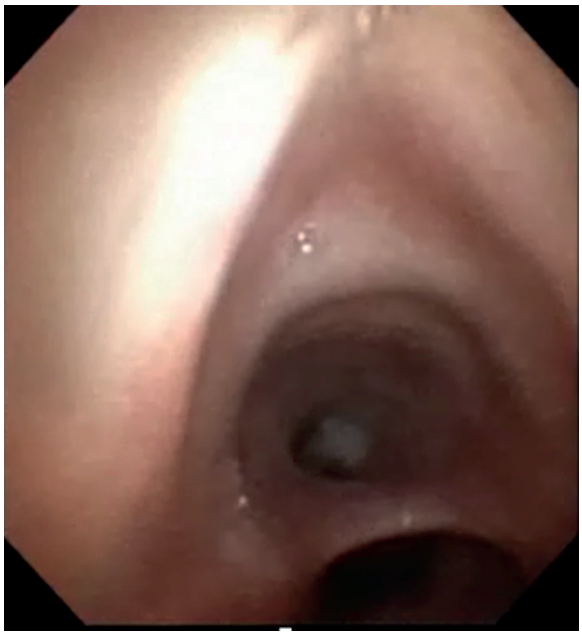

***Figure 3**. Bronchoscope image of a 3-week-old baby with recurrent aspiration: Connection is visible between the trachea and the esophagus creating a laryngotracheoesophageal cleft.*

The diagnosis can be missed with flexible bronchoscopy as it may be difficult to see the defect due to abundant tissue. Flexible and rigid bronchoscopy should be combined to exclude laryngotracheoesophageal clefts (41).

Congenital TOF

Most cases of congenital TOF are associated with esophageal atresia and a fistulous connection between the trachea and esophagus that can be proximal, distal (most common type, near the carina) or both (21, 42). A laryngeal cleft might also be present in these cases.

Esophageal atresia occurs more rarely without a fistula, and in this situation, there is absent gas in the gastrointestinal (GI) tract after birth. The diagnosis of an H-type fistula without esophageal atresia is often delayed and can present much later. This may be a difficult diagnosis as it can easily be missed on both contrast study and bronchoscopy.

Anomalies of the VACTERL spectrum as well as both tracheal and esophageal stenoses are associated with TOF (21).

Congenital broncho-esophageal fistula (BOF)

Congenital BOFs were first described by Negus in 1929 (43). In 1965, Braimbridge and Keith classified

it into four categories (44). This is a rare diagnosis and even more rare in young children with about 100 cases have been reported in the literature in mostly adult patients. The presentation may be delayed until childhood or adult life, with a median age of 33 years old, while the duration of symptoms can vary from 6 months to 50 years, with a mean of 17 years (45, 46). The majority (90%) of fistulas are type II according to the Braimbridge classification (47).

The communication is usually short and is running directly from the esophagus to a main or segmental bronchus. Conventional barium esophagography is the most sensitive and most "rewarding" tool in the diagnosis of BOFs (45, 47). In other types, the fistula is communicating with a congenital esophageal diverticulum (type I), an intralobar cyst (type III) or a pulmonary sequestration (type IV) (43).

EXTERNAL AIRWAY COMPRESSION

Bronchogenic cyst

Bronchogenic cyst (BC) are mostly single, unilocular cysts which is filled with fluid or mucous. The BC arise from abnormal budding of the primitive trachea-bronchial tree during airway development, but do not branch further and end as a blind pouch (48).

BC most commonly occur in the mediastinum adjacent to one of the mainstem bronchi but can occur anywhere throughout the thoracic cavity including the retroperitoneum, neck, tongue, and subcutaneous tissue. About 65% to 90% of BC occur in the paratracheal, subcarinal, or hilar regions (48, 49). The most common location is subcarinal followed by the right paratracheal region (50). Intraparenchymal BC are found in approximately 12% of cases (51). They are lined by pseudostratified ciliated columnar respiratory epithelium and contain hyaline cartilage plates (48). Parenchymal BC have no communication between the cysts and the tracheobronchial tree. Communication of mediastinal BC with airways have rarely been reported (52). Expanding BC can cause central airway obstruction due to mass effect with or without distal lung hyperinflation. Due to mucus built-up, the cyst can enlarge and lead to infection. Infected BCs are more often found in older children and adults than in neonates or infants (12, 53). BC can be diagnosed on antenatal ultrasound and confirmed on CT scan after birth.

Foregut duplication cysts

Esophageal duplication cysts are rare congenital cystic masses which result from an error in foregut budding in the 4th to 6th week of embryonic development. The incidence remains unknown but the reported incidence from autopsies is 1 in 8200 autopsies (54).

William E Ladd used the term "duplications of the alimentary tract" in 1937 and he applied the term to congenital lesions having: (1) the presence of a well-developed coat of smooth muscle; (2) an epithelial lining representing some type of intestinal tract mucosa, and (3) intimate anatomic association with some portion of the gastrointestinal tract (55).

The foregut budding defects may lead to either a BC, esophageal duplication cyst, or "bronchopulmonary foregut malformations" (BPFM) (56).

Duplication of the cervical portion of the embryonic foregut accounts for 23% of all esophageal duplications and present as either an enlarging neck mass or with upper airway obstructive symptoms. They can also be asymptomatic. Duplication cysts of the mid esophagus constitute 17% of esophageal duplications and in the lower third in 60%. Esophageal duplication cysts can present with respiratory distress due to mass effects and compression on the large airways.

Airway compression is more often seen with BC compared to foregut duplication cysts due to their close location to the large airways (57).

Esophageal duplication cysts are difficult to diagnose on chest X-rays as the features are similar to that of the BCs but with the wall of the esophageal duplication cyst in more close contact with the esophagus.

Duplication cysts may be a rounded mass, with uniform density similar to that of the cardiac shadow and located close to the mediastinum. Air-fluid levels may be seen if the lesion communicates with the tracheobronchial tree (58).

A CT or MRI is needed for diagnosis and soft-tissue characterization. A CT scan can show a water attenuation structure which is located close to the esophagus. Early surgical resection is indicated to prevent recurrent or persistent pulmonary infection (59).

Vascular compression

The airways of young children are more pliable and smaller than those of adults. This makes them more likely to be symptomatic from extrinsic airway compression

(60). Vascular airway compression occurs with several entities associated with enlarged, malpositioned or encircling central vessels (so called rings and slings) (21, 61).

Double aortic arch

Double aortic arch (DAA) (**Figure 4A-F**) is the most common cause of vascular compression of the airway in children (62-64). DAA is determined by the presence of both left- and right-sided aortic arches, which together surround the trachea and esophagus. The right arch is usually the larger ('dominant') one and the left arch is usually small ('hypoplastic') or forms a fibrous cord ('atretic' segment) beyond the origin of the left common carotid or subclavian artery (65). The fibrous cord tethers the patent part of the left-sided arch to the descending aorta, completing the ring. A ductal ligament connects the distal left arch to the proximal LPA and form a ring. The fibrous cord is normally not seen on imaging and the diagnosis is made on the presence of an incomplete left arch (65). The presence of this diverticulum implies the presence of a non-visualized ductal ligament along with a vascular ring (66).

Depending on the type, the descending aorta may be left- or right-sided or may run in the midline anterior to the vertebral column. With the descending aorta midline, the structures of the mediastinum are 'stacked', resulting in compression between the spinal column and the sternum (67).

DAA presents in infancy, with symptoms including dysphagia, stridor, wheezing and respiratory distress (68). Transection of the non-dominant arch is required to relieve the airway compression (69). It is important to diagnose the arch anatomy before surgery because this determines the operative approach. Thirty percent of children will have residual symptoms despite surgical treatment. The residual symptoms may be due to persistent airway compression or severe malacia of the lower trachea (67).

Left pulmonary artery sling

In the PA sling anomaly, the Left pulmonary artery sling (LPA) arises from the RPA and courses to the left hilum between the trachea and esophagus.

There are 2 types of LPA: Type 1, position of the carina is usually normal, at the T4-T5 level and Type 2, low position of the carina, typically at the T6 level. In type 1 the airway is usually not stenotic, but the right bronchus might be compressed by the sling.

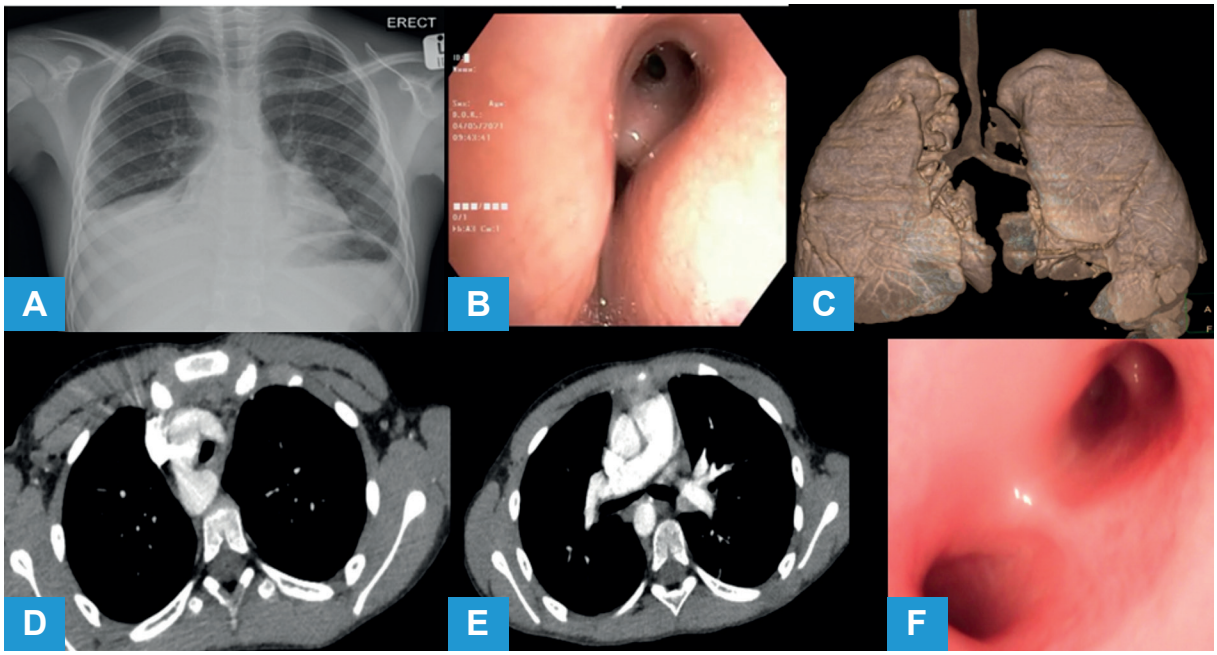

***Figure 4**. 8-year-old boy, who had previous surgery for double aortic arch presented with: (**A**) collapse of the RML and RLL on the chest X-ray; (**B**) bronchoscopy image demonstrates compression of the opening of the RMB; (**C, D, E**) chest CT scans confirms large right-side arch causing distal trachea and RMB compression. The descending aorta (**E**) running on the right side also causes compression of the right main bronchus; (**F**) bronchoscopy image during posterior aortopexy showing that the compression has significantly improved.*

Long-segment tracheal stenosis due to complete cartilaginous rings, T-shaped carina, and a bridging bronchus are often seen in patients with type 2 PA sling (20, 31, 70) (**Figure 5**). Type 2 is often associated with congenital cardiac anomalies.

LPA is suspected based on careful evaluation of plain radiographs and especially recognition of a narrowed or poorly visualized airway with a low horizontal bifurcation, right lung overinflation or hypoplasia. CT angiography is the most common study of choice to fully define the vascular and airway anomalies.

The LPA is reimplanted onto the left side of the main PA and sliding tracheoplasty is the technique of choice for long-segment tracheal stenosis.

Left main bronchus vascular compression

The left main bronchus (LMB) has a longer course and a smaller diameter than the right main bronchus and is wedged between the PA anteriorly and the esophagus, descending aorta (DA) and vertebral body posteriorly (71). Vascular compression of the LMB in the absence of cardiac disease is at least in part, related to an anteriorly positioned DA. The prespinal position of the DA has also been noted as a normal variant in asymptomatic children. Bronchoscopy demonstrate medial and lateral compression with pulsation of the LMB just after the off take of the LMB. The airway distal to the area of compression is normal (72, 73). At surgery a ligament or patent ductus arteriosus remnant can be identified pulling the PA and DA to each other and trapping the LMB (74).

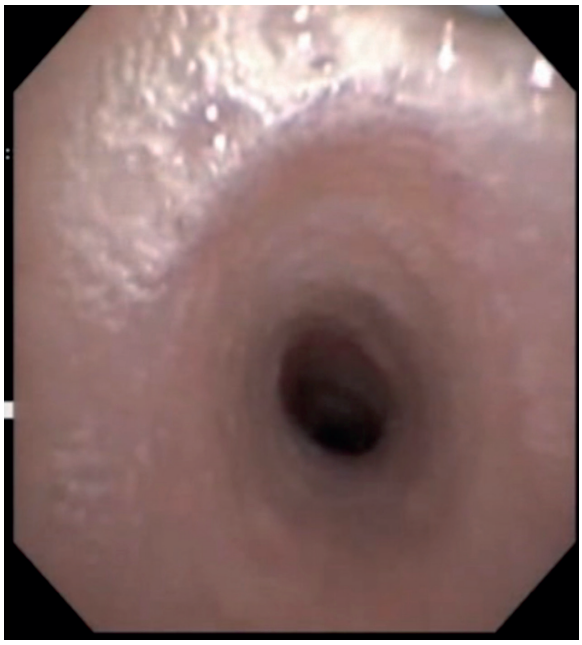

***Figure 5**. Bronchoscopy image demonstrate solid tracheal rings confirming congenital tracheal stenosis.*

Innominate artery compression

Anterior compression of the trachea by the brachiocephalic trunk (Innominate artery compression - IAC) is a commonly seen on bronchoscopy. This is due to the innominate artery as it crosses from left to right and symptoms similar to those who do have a vascular ring (75). This condition seems to have been over-diagnosed and possibly over-treated in the past. IAC needs to be differentiated from tracheomalacia as seen in esophageal atresia (76). Stacking may also play a role with a large thymus pushing the innominate artery onto the anterior part of the trachea.

Operative intervention is indicated for patients with more than 80% compression of the tracheal lumen, as measured on bronchoscopy (77). The innominate artery is suspended to the sternum, with multiple techniques. Anterior thoracotomy can be used with removal of part of the thymus.

Intraoperative bronchoscopy confirms successful pexy and opening of the compressed trachea.

Other causes of vascular compression

- **Interrupted aortic arch (IAA)**. Some part of the lumen of the aortic arch is discontinuous and is found in about 1% of all children with CHD. The airway compression seen in IAA is a consequence of surgical repair and mostly not related to the malformation (14).
- **Right-sided aortic arch (RAA)** with an aberrant left subclavian artery. RAA with an aberrant left subclavian artery and/or a left *ligamentum arteriosum* is reported in 12%-25% of children with vascular rings. These children are mostly asymptomatic. The left subclavian artery often originates from an outpouching of the descending aorta, called a Kommerell's diverticulum. If airway compression is present, it is due to airway compression in the RAA and is usually due to the enlargement of the Kommerell's diverticulum, a short *ligamentum arteriosum* or a midline descending aorta (78).
- **Absent pulmonary valve (APVS)**. It is characterized by the presence of enlarged PAs and hypoplastic pulmonary valve cusps. It is seen in association with ventricular septal defect and right ventricular outflow tract obstruction (14). Compression of the

lower trachea, LMB and right main bronchus or bronchus intermedius occurs due to enlargement of the PAs and left atrium (79, 80).

HORSESHOE LUNG

Horseshoe lung is a very rare congenital malformation in which the bases of the right and left lung are fused to each other by a narrow isthmus. Although rare, a hyperlucent area in the lower left lung, close to the vertebral column, may represent a horseshoe lung. Horseshoe lung is often associated with scimitar syndrome (81). There may be an aberrant RLL bronchial branch which supply the horseshoe segment of the right lung.

TRACHEOBRONCHOMALACIA

Tracheomalacia (TM) is the most common congenital tracheal abnormality with a reported incidence of 1 in 2,100 children (82, 83). Tracheobronchomalacia (TBM) has been often reported in infants and young children who underwent bronchoscopic evaluation for respiratory distress. TM is an abnormal softness of the tracheal wall due to structural anomalies of tracheal cartilaginous and/or posterior membrane. The ratio among cartilage and the floppy part of the normal trachea is around 4.5/1. The symptoms are thought to often be incorrectly attributed to asthma.

TM is difficult to diagnose due to dynamic airway narrowing. Diagnosis of TM is based on dynamic trachea-bronchoscopy with direct observation of the tracheal collapse during spontaneous breathing. The aim of bronchoscopy is to evaluate the percentage of reduction of airway lumen and the sites involved (upper, middle, distal trachea, proximal and peripheral bronchi). TM may be either primary (congenital) or secondary (acquired). Primary TBM is caused by impaired cartilage maturation or cartilage deficiency and is relatively uncommon. Primary or congenital TM/TBM can be found alone or in conjunction with other genetic and congenital disorders (84, 85). TM is associated with morphogenetic airway anomalies including tracheoesophageal fistula, esophageal atresia, mucopolysaccharidoses and polychondritis.

Bronchoscopy and inspiration/expiration CT imaging are used to evaluate airway collapse in expiration. Caliber change of >50% between inspiration and expiration is the criterion for diagnosis of TM (21).

AIRWAY ABNORMALITIES ASSOCIATED WITH CONGENITAL HEART DISEASE

Airway abnormalities are important but sometimes overlooked problems in children with congenital heart disease. It is often difficult to separate symptoms related to cardiac disease from those associated with airway or lung disease. Some of the lesions are incidental while others cause significant symptoms and are important in overall functional outcome. Congenital and acquired as well as intrinsic and extrinsic lesions occur and can overlap.

CONCLUSIONS

Infants with stridor, abnormal cry, feeding difficulties, and signs of airway obstruction should be evaluated with an awake flexible laryngoscopy and, if necessary, a direct laryngoscopy or bronchoscopy. The diagnosis of congenital airway anomalies requires a high degree of suspicion. Treatment often involves a multidisciplinary team approach given the rate of associated abnormalities and complexity of disease.

COMPLIANCE WITH ETHICAL STANDARDS

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Author contributions

Prof. PG, Dr. DR, Dr. AG and Prof. JJ are the only Authors responsible for the conception and design of the work as well as the acquisition, analysis and interpretation of data presented.

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N/A.

Data sharing and data accessibility

The data underlying this article are available in the article.

Publication ethics

Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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REVIEW

Congenital pulmonary airways malformation: state of the art review

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ABSTRACT

Congenital pulmonary airway malformations (CPAM) are rare anomalies of the lung development, arising during intra-uterine life. Currently, CPAM are diagnosed prenatally, due to improved imaging techniques. They may be asymptomatic or cause a broad range of symptoms. Symptomatic lesions require treatment, which might be performed during fetal period or after birth. Surgical options vary from minimally invasive to open surgery. Concerning the long-term assessment of respiratory function after lung resection, long-term outcome studies are still lacking. A multi-disciplinary team play an essential role in ensuring that the patients affected by CPAM receive the most appropriate treatment and follow-up to preserve the lung function.

IMPACT STATEMENT: The purpose of this revision is to clarify the still controversial management of congenital pulmonary airways malformation in pediatric age.

KEY WORDS
Congenital pulmonary airway malformations; prenatal diagnosis; surgical options; lung function.

INTRODUCTION

Congenital pulmonary lesions (CLL) are heterogeneous group of rare pulmonary parenchymal abnormalities, including congenital pulmonary airway malformations (CPAM), bronchopulmonary sequestration, bronchial atresia, and congenital lobar emphysema (1).

CPAM are quite rare congenital malformations. Their incidence is between 1:25,000 to 1:35,000 (2). Thanks to increasing prenatal diagnoses, the most recently estimated incidence has increased up to 1 out of 7200 births (3).

CPAM are hamartomatous lesions lined by respiratory epithelium which include cystic and adenomatous elements derived from the tracheal, bronchial, bronchiolar, and alveolar tissue with an abnormal and disorganized growth of the terminal bronchioles (3, 4).

They may be asymptomatic or cause symptoms since the first months of life. These lesions are mainly diagnosed during childhood, even if they are sometimes associated with lung cancer in adults (3).

The underlying pathogenesis require the interplay of multiple regulatory factors, whose involvement in pulmonary malformations still remain uncertain. According to an *environmental hypothesis*, the expression of genetic defects associated to the lung development correlates to a focal and temporary disruption of the lung morphogenesis (4). Supporting this theory, multiple genes involved in cell proliferation/

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apoptosis could be implicated in the process, including thyroid transcription factor gene (Nkx2), Sonic Hedgehog (SHH), Sprouty 2 (SPRY2), Bone Morphogenetic protein (BMP4), Wnt signaling pathways, transforming growth factor β (TGFβ), and fibroblast growth factors 10, 9, and 7 (FGF10, 9, 7) (4). Recently, the *obstructive hypothesis* has been also proposed. According to this hypothesis, the focal obstruction of airways would increase levels of mediators associated to dysplasia found in CPAM (4, 5).

CLASSIFICATION

The most common classification proposed by Stocker *et al.* (6) initially identified three groups of lesions: type 1, the most frequent form, with large cysts containing mucous cells; type2, characterized by multiple small cysts; type 3, with large solid lesions with mediastinal displacement. In 2001, this classification was updated with new types of lesions such as type 0 (acinar dysplasia) and type 4 with cysts lined by alveolar cells without mucous cells (4).

Recently, this model has been questioned since several studies have suggested that the Stocker's classification may not accurately describe the histopathology of CPAM detected during prenatal period (7, 8). Indeed, congenital lung malformations could usefully be classified into three groups, based on their initial radiographic results (see **Table 1**), congenital solid/cystic lung abnormality, congenital hyperlucent lobe, and congenital small lung, respectively (5, 8).

The first group (congenital solid/cystic lung abnormality) includes congenital pulmonary airway malformations, intra and extra lobar sequestrations, bronchial atresia, bronchogenic cyst, mixed malformations. According to the Author (5), all the masses within this group should be associated to abnormal arterial/venous drainage and might also retain a primitive foregut connection. The second one (congenital hyperlucent lobe) includes congenital lobar emphysema and multi-alveolar lobe. These lesions may have a common etiology that leads to airway obstruction with distal air trapping. Lastly, the third group (congenital small lung) includes lung/lobar agenesis and pulmonary hypoplasia associations (5).

In addition, as proposed by Adzick *et al*. (7), a further clinical classification of CPAM is based on the size of the lesions at pre-natal ultrasound, dividing them into macrocystic (75%) with a diameter ≥5 mm and microcystic with the appearance of a solid mass (25%) ≤5 mm.

***Table 1**. Simplified classification of congenital lung malformations based on radiographic results.*

Group 1 (Congenital solid/cystic lung malformation)
• Congenital pulmonary airway malformation
• Intra and extra lobar sequestration
• Bronchial atresia
• Bronchogenic cyst
• Mixed malformations
Group 2 (Congenital hyperlucent lobe)
• Congenital lobar emphysema
• Polyalveolar lobe
Group 3 (Congenital small lung)
• Lung/lobar agenesis
• Pulmonary hypoplasia associations

CLINICAL PRESENTATION

Generally, CPAM are asymptomatic malformations (2, 4, 9). Conversely, when the fluid contained in the lesion is replaced with air, the lung compression leads to respiratory distress, immediately after birth or in the first days of life (9). According to recent studies (9), about 25% of asymptomatic patients with prenatal diagnosis of CPAM develop symptoms for the first time around the age of 6-7 months. In addition, CPAM may become symptomatic when lung infection occurs later in life. In fact, the malformation itself becomes a focus of infection, thus making patients more susceptible to recurrent pneumonia in the first months of life (9). The clinical presentation with pneumothorax or hemothorax is very rare but already described in literature (10-12). If early frequent pulmonary infections should arise the clinical suspicion of CPAM, on the other hand wheezing is more frequent in patients antenatally diagnosed and not operated (4).

DIAGNOSIS

The use of antenatal ultrasound screening has allowed the early detection of congenital lung abnormalities that would not have been diagnosed unless they become symptomatic (5).

The prenatal diagnosis of congenital cystic lung lesions reaches a percentage of 85.7% through ultrasound. The average gestational age at which these malformations can be detected is the second trimester (21-24 weeks), when the CPAM appears as an echogenic mass within the fetal lungs (4).

The role of prenatal magnetic resonance (MRI) is increasingly preponderant, as it is able to detect all types

of fetal malformations with a sensitivity and specificity of 95%. MRI seems to be the best technique to better identify hybrid lesions (4). MRI is also useful in the differential diagnosis between CPAM and other intra-thoracic lesions, allowing to define the exact location of the lesion within the pulmonary lobe and the presence of lung compression (7). However, both prenatal US and MRI show high accuracy in the detection of isolated lung malformations (4, 13).

The initial evaluation should also include fetal echocardiography, since the incidence of structural and functional cardiac anomalies is increased in these patients, affecting prenatal surgical treatment (4, 7).

Once the prenatal diagnosis of CPAM has been made, it is necessary to carry out serial ultrasound screening in order to monitor the possible appearance of hydrops fetalis, mediastinal displacement and esophageal compression (4, 7). Crombleholme et al. developed the CPAM volume ratio (CVR) score to identify fetuses at risk of complications: it is a measure of the lesion volume, normalized by gestational age. Recent studies have shown that a CVR ≥ 1.6 was highly predictive of hydrops and that a CVR ≥ 0.84 was associated with polyhydramnios and ascites increasing the risk of severe respiratory distress. The purpose of this score is to establish a predictive tool for potential life-threatening complications and to provide an adequate therapeutic approach. In fact, even if 70% of CPAM antenatally diagnosed are asymptomatic at birth, the remaining 30% present with respiratory distress requiring assisted ventilation in 10% of cases (4, 13).

CPAM may undergo spontaneous involution, which has been reported in up to 49% of cases beyond the 28 weeks of gestation (2, 4, 7). Evanescent lung lesions seem to be a frequent finding, especially if they are microcystic and low volume lesions (4,7). Even if we are dealing with a lesion that disappeared during pregnancy, radiological investigations are recommended at birth (7). To avoid exposing the newborn to frequent radiation doses, it would be advisable to carry out a chest X-ray at birth and further scans (X-ray or computed tomography angiography, CTA) within 6 months of life (4). During postnatal follow-up, MRI should be an alternative to a CT scan after surgical resection and even in case of asymptomatic stable lesions (14).

After birth, clinical presentation ranges from being asymptomatic to respiratory failure. In asymptomatic children, the diagnosis of CPAM should be made after incidental findings on chest radiological imaging performed for other medical indications such as a pulmonary infection or thoracic pain (4, 12).

Moreover, several cases have shown the possibility that lesions firstly defined as CPAM were later diagnosed as pleuropulmonary blastoma (PPB) (15-16), confirming that the misdiagnoses are quite common and that it is essential to plan an adequate follow-up over time, in order to avoid misdiagnoses (12). Numerous studies have confirmed the relationship between DICER1 gene mutations and oncogenesis of a range of neoplasms (17), including PPB and DICER1 genetic analysis should be performed especially in cases of challenging differential diagnosis.

PRENATAL TREATMENTS

The indications for fetal surgery are extremely rare and based on the pathophysiologic consequences of lung lesions large enough to compromise adjacent organs (14). In fact, mediastinal shift, pulmonary hypoplasia, polyhydramnios, cardiovascular compromise, or esophageal compression require a prenatal management (2). Maternal steroids, thoraco-amniotic shunts, fetal mass resection, and *ex utero intrapartum* treatment (EXIT) procedures play a significant therapeutic role in congenital lung lesions with hydrops, resulting in lower risk of prematurity, less ventilator requirement, and a better outcome, compared to open or minimally invasive fetal surgery (18-22).

In macrocystic lesions, thoracocentesis or thoraco-amniotic shunting are useful for both diagnosis and treatment of hydrops. The indications for open fetal surgery are hydrops and signs of evolving fetal heart failure (20). For fetuses with large masses inducing mediastinal shift, when lung development is compatible with life, the EXIT procedure is a therapeutic option performed in highly specialized centers (21). When treatment possibilities are overcome, a therapeutic abortion can be discussed (22).

POSTNATAL MANAGEMENT

Newborns with respiratory symptoms, including cyst infection, hemorrhage, dyspnea, pneumothorax, nutritional problems, sudden respiratory compromise, and malignant transformation (type 4 CPAM *versus* type I cystic pleuropulmonary blastoma, PPB) require a timely surgical treatment (23-27).

Asymptomatic patients are approximately three quarters of children with a prenatally diagnosed lung malformation.

Prior to discharge, newborns need to do a chest X-ray to establish a baseline for subsequent imaging (24). A multidisciplinary follow-up with a pediatric pulmonologist and surgeon is recommended. The gold standard diagnostic test for evaluating a lung lesion is a chest CTA within six months of life. The role and timing of surgery in asymptomatic lung lesions remains controversial (25).

Surgery in asymptomatic patients can be performed safely with few post-operative complications and planned at a young age in patients with a high risk of developing clinical signs later in life (20). Patients with CPAM appear to have better perioperative outcomes before the beginning of symptoms, including shorter operating times, shorter post-operative mechanical ventilation, shorter chest drainage duration and shorter post-operative hospital stays (23).

The decision to undergo surgery is based on clinical evolution and/or to prevent complications, such as pneumonia refractory to antibiotics due to impaired muco-ciliary clearance of the lesions and tumorigenesis due to chronic inflammation (25, 26).

The best timing for elective surgery of asymptomatic infants is still debated but seems to be between 6 months and 2 years old, in order to maximize the compensatory lung growth and because approximately 25% of originally asymptomatic patients develop symptoms at around the age of 6-7 months (9, 27-29). Indeed, the timing of the surgical treatment depends on the clinical conditions of the patient. In case of respiratory distress, the surgery will be performed urgently, otherwise the surgical treatment can be postponed until 12-18 months of life (23-28).

Currently, thoracoscopy is considered the preferred surgical approach over the standard thoracotomy, with reduction of post-operative complication and musculoskeletal deformities (30-32). Pulmonary resection via conventional open thoracotomy may be performed using a muscle sparing technique, which is associated with relatively lower long-term musculoskeletal morbidity (32).

The thoracoscopic intervention is difficult in neonates because of the small exposure space. Video-assisted thoracoscopic surgery was reported to be safe and effective, even in infants less than 3 months of age when performed in experienced centers (33).

The choice between lobectomy or partial lobectomies (*e.g.*, segmentectomies, wedge resections) should be guided by the extension of the lesion which should be completely removed, sparing as much lung parenchyma as possible (2, 20, 34).

NATURAL HISTORY AND CLINICAL OUTCOME

Children with congenital malformations affecting lung development are at risk of short and long-term respiratory complications, especially in the first years of life. At least three quarters of patients with a prenatal diagnosis of CPAM are asymptomatic at birth. For these patients the clinical management is still controversial (34). Given the prognostic implication of neoplastic transformation, the identification of DICER 1 mutations could be useful to identify who undergo early surgery among totally asymptomatic patients (17, 35, 36).

Even if an early resection should lead to a better compensatory growth, surgery is not the universally accepted choice in case of asymptomatic lesions (25). On the other hand, the recurrent infections and the related tissue inflammation are the most important factor in influencing the timing of surgery (36).

As reported by Zeng *et al*., the early surgical treatment should be performed within 2 years of age, considering the high risk of infection and more invasive surgery (34). Beyond pulmonary infections and reduction of pulmonary function, the risk of malignancy development should be an incentive for prophylactic excision of asymptomatic CPAM (34).

The natural history of patients who did not undergo surgical treatment is poor understood (25, 37). Even if many CPAMs remain asymptomatic for years (38, 39), endorsing a “wait and see” approach, the operative complication rate increases as lesions become symptomatic, thus requiring urgent surgery (37). This evidence could suggest an elective surgical treatment.

In case of surgical treatment, early post-surgical complications (*e.g.*, includes pneumothorax, pleural effusion with subcutaneous emphysema and respiratory distress) may not be related to a specific surgical approach or to the surgical technique (40). Long-term complications (*e.g.*, chronic cough, recurrent lower-airway infections, wheezing, poor tolerance to exercise, or orthopedic impairments) show up with high prevalence during post-surgery follow-up (41).

Concerning the long-term assessment of respiratory function of children who underwent surgery for lung resection, the literature shows a lack of long-term out-

come studies into adulthood. Most studies used respiratory function as a surrogate marker for lung growth and volume. Lam *et al.* (32) performed a direct comparison between thoracoscopic and open lobectomy to test for any difference between the surgical approaches, evaluating long term pulmonary function test (PFT). Even if most patients from both groups have normal long term PFT results, up to 10% of them developed subclinical impairment of PFT (restrictive pattern) (32). Generally, Total Lung Capacity (TLC) is preserved at long term follow-up and may even be more than expected. The elevated residual volumes and functional residual capacity found after lobectomy advocates that overexpansion of residual lung may be compensating for loss of tissue and contributing to TLC, rather than true lung growth (42).

CONCLUSIONS

Great improvements have been made in the understanding of CPAM features. Its clinical detection is almost done prenatally, even if the diagnosis can be made accidentally in the postnatal period based on respiratory symptoms and radiological imaging (**Figure 1**).

The indication for surgery is widely supported for symptomatic lesions. Conversely, the management of asymptomatic lesions is still debated.

Notably, elective surgery reduces the risk of infections and pneumothorax, improves compensatory lung growth, and prevents the risk of neoplastic degeneration (carcinoma, pleuropulmonary blastoma).

A multi-disciplinary team should play an essential role in ensuring that the patients affected by CPAM receive the most appropriate treatment and follow-up to preserve the lung function (**Infobox 1**).

Infobox 1. *Educational aims.*

Box 1. Educational Aims

- CPAM are quite rare congenital malformations
- The diagnosis of congenital cystic lung lesions is almost prenatal
- The decision to undergo surgery in symptomatic patients is based on clinical evolution and/or to prevent complications
- The best timing for surgery of asymptomatic patients is still debated
- A multi-disciplinary team should play an essential role in ensuring that the patients affected by CPAM receive the most appropriate treatment and follow-up to preserve the lung function

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

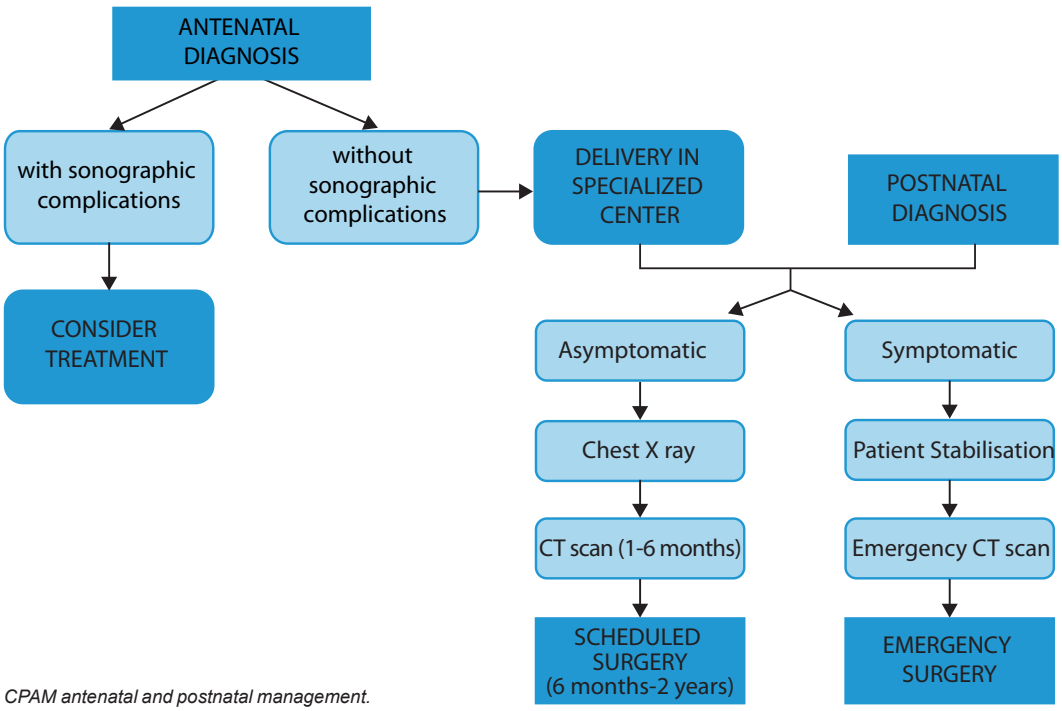

Figure 1. *CPAM antenatal and postnatal management.*

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Author contributions

RL, MG and ED: conceptualized the study, drafted the initial manuscript, reviewed the literature and critically revised the final manuscript. GC and AR: contributed to the review of the literature. They also actively participated in manuscript drafting, critically reviewing it. All Authors read and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical approval

Human studies and subjects

N/A.

Animal studies

N/A.

Data sharing and data accessibility

All the data are available in the article.

Publication ethics

Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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REVIEW

Effects of home wall painting on respiratory and allergic diseases in children

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ABSTRACT

The effect of household air pollution on health is an important topic of study and research considering the increasing amount of time that people spend inside buildings. Although numerous studies have been conducted on indoor allergens and their effects on the development of allergies in both adults and children, little is known about the pollutants produced by indoor painting and their association with respiratory diseases.

Recent studies have suggested a significant cause-and-effect correlation between high VOCs concentrations in indoor air, due to repainting, and the development of respiratory and allergic diseases in children, while other papers report the absence of effects on health when paints with low VOCs concentrations are used. However, the evidence is currently insufficient to draw firm conclusions, and further high-quality observational studies, as well as clinical trials, are needed for a more comprehensive investigation to elucidate this issue.

Given the potential risks in both the development of fetuses and children, it is imperative that government agencies and organizations implement proactive measures on wall paints to prevent potential adverse health outcomes.

IMPACT STATEMENT: Little is still known about the correlation between air pollution due to indoor wall painting and the development of allergy and respiratory diseases in children. Many components derived from paints can stimulate the airways, particularly in children. Proactive initiatives are necessary to protect fetuses and children from these indoor pollutants.

INTRODUCTION

During the last decades, the life of people has experienced profound transformations caused by industrialization, urbanization, and fuel fossils consumption. All these factors have led to a dramatic increase in air pollutants, including particulate matter (PM), nitrogen dioxide (NO_2), ozone (O_3), affecting both human health and the entire ecosystem (1).

With the increasing concentration of air pollutants, it has also been registered a rapid increase in the prevalence of allergic diseases, such as asthma, allergic rhinitis, atopic dermatitis and food allergies.

Notably, childhood asthma is emerged as a pressing public health concern, with compelling evidence suggesting its potential to persist into adulthood and even develop into chronic obstructive pulmonary disease (COPD) (2).

ABBREVIATIONS LIST

AD: Atopic Dermatitis; CI: Confidential Interval; COPD: Chronic Obstructive Pulmonary Disease; EEA: European Environment Agency; EJ: Environmental Justice; EPA: Environmental Protection Agency; IAC: Indoor Air Comfort; IAQ: Indoor Air Quality; IED: Indoor Environments Division; HDM: House Dust Mites; MIT: Methylisothiazolinone; OR: Odd Ratio; TEAM: Total Exposure Assessment Methodology; TVOCs: Total Volatile Organic Compounds; VOCs: Volatile Organic Compounds.

KEY WORDS

Wall paint; allergy; respiratory diseases; children; VOCs.

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While many studies focused on infectious agents and on allergens in the domestic environment, such as proteins derived from mites, cat, dog, cockroaches and fungi, the need to prevent the development of asthma and allergic diseases in children has stimulated research into other potential indoor and outdoor environmental causes (3), such as volatile organic compounds (VOCs), namely a group of molecules having at 293.15 K a vapor pressure of 0.01 kPa or more (4). Household products, such as glues, cleaners, and paints, have been identified as significant contributors to indoor air pollution, releasing VOCs and other chemical molecules that may have adverse health effects (3, 5). Even though children spend the majority of their daily time indoors (6-8), nowadays there is insubstantial knowledge about chemical indoor pollutants and their correlation with diseases developed during childhood. Actually, a limited number of studies explore the potential correlation between chemicals or fine particles emission resulting from painting walls and the possible effects on respiratory and allergic diseases in children (9, 10), and even less studies take in account the correlation between VOCs concentration in the paint with health diseases, whereas paint companies have already started to offer products with lower VOCs concentration. The aim of this paper is to review the latest scientific medical literature on the effect of home wall painting or repainting on respiratory and allergic diseases, such as asthma, atopic dermatitis and rhinitis, in children.

METHODS

Databases and keywords

PubMed, Embase and Cochrane databases have been used to find the most relevant studies conducted within the last 16 years (from 2006 to 2022).

The keywords used were: “indoor wall painting”, “indoor wall repainting”, “indoor wall paints AND allergy AND children AND airway disease”.

The articles have been selected with the following criteria:

– publications in scientific medical journals with peer-review;
– papers including, among the objects of the study, also the components of the internal wall paintings of the houses;
– papers including mould and moisture in indoor environment;
– papers studying the correlation between components of internal wall paints and respiratory and/or allergic diseases;
– paper identifying the risks with “Odd ratio” (OR) and confidence interval (CI);
– relevant papers identified from citation searching;
– articles relating to the “sick building syndrome” have been excluded because they are much discussed as a nosological entity and not recognized as such by some authoritative scholars;

RESULTS

With these criteria, 251 publications were extracted and among them 34 were in compliance with the inclusion criteria. The selection criteria are detailed following PRISMA guidelines in flowchart of **Figure 1**.

Amongst the studies which have been more accurately analyzed for their content, there were:

– 15 epidemiological or cohort studies, among them the most relevant have been reported in **Table 1**;
– 10 reviews, among them the most relevant have been reported in **Table 2**;
– 3 studies on the evaluation of indoor air quality and 1 on “green homes”;
– 4 publications on indoor air quality (IAQ) and Atopic Dermatitis (AD) (**Table 3**).

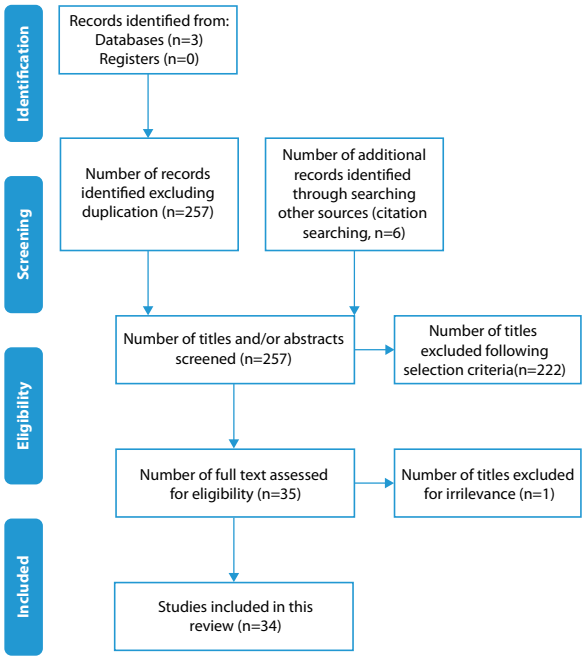

Figure 1. *PRISMA flowchart.*

This is a narrative review and no meta-analysis has been performed. However, in order to be more informative, odds ratios and CI of the health outcomes associated with environmental exposure for the selected studies have been reported.

INDOOR AIR POLLUTANTS

From the analysis conducted by the selected articles, it emerged that the most frequent indoor air pollutants are: moulds, VOCs (volatile organic compounds), PEGs (polyethylene glycols), and isothiazolinones (**Table 4**).

Table 1. *Most significant Cohorts and multi-center studies.*

No of subjects	Pollutant	Effects	Results	Ref.
10,851 children	VOCs (PEG)	Asthma, hyperhidrosis	OR = 2.779 (CI = 1.33-5.80) *	#7
31,742 children	Mould	Asthma, allergic rhinitis	OR = 1.18 (CI = 1.09-1.28)	#12
863 children	VOCs	Allergy to HDM	OR = 1.40 (CI = 1.10-5.30)	#16
172 children	Low VOCs (PEG)	Wheezing, asthma	OR = 1.16 (CI = 1.03-1.29)	#23
462 students	Para-dichloro benzene	Asthma	OR = 1.16 (CI = 1.06-1.27)	#26
163 children	VOCs from paint	Asthma attacks	OR = 10.49 (CI = 1.16-94.85)	#27
1048 students 12-15 years old	Unspecified	Asthma	OR = 1.71 (CI = 1.60 – 2.7)7	#28
235 partecipants	Green homes	Diminished risk of asthma	Asthma: OR = 0.34 (CI = 0.12-1.00) Less asthmatic attacks: OR = 0.31 (CI = 0.11-0.88) Less absence from school due to asthma: OR = 0.21 (CI = 0.06-0.74)	#30

* This data refers to the exposition to wall paint.

Table 2. *Most relevant reviews.*

No of studies	Pollutant	Effects	Ref.
48	VOCs	Asthma and allergy in children and adults, no clear conclusions	#5
61	Moulds	Asthma (OR = 1.49; CI = 1.28-1.72), wheezing (OR = 1.68; CI = 1.40-1.90) allergic rhinitis (OR = 1.39; CI = 1.28-1.51)	#8
21	Aldehydes, aromatic hydrocarbons, aliphatic hydrocarbons, other VOCs	Exacerbation of asthma and irritation of the lower airways, in children and adults	#10
37	VOCs and S-VOCs	Childhood bronchial asthma	#13
20	VOCs	Uncertainty about the effect of most VOCs as cause or aggravating agent of asthma in children and adults	#21
53	VOCs	Weak evidence that VOCs have a role in the development of asthma and allergic diseases in adults and children and in their exacerbations	#22
17	VOCs	VOCs that could favour allergic and respiratory diseases	#32

Table 3*. Most relevant studies on indoor air quality and Atopic Dermatitis (AD).*

No of subjects	Redecoration activities	Effects	Results	Ref.
20,687 children	House painting during pregnancy	Increase risk of AD	Renovation: OR = 1.61 (CI = 1.27-2.02) House painting: OR = 1.72 (CI = 1.30- 2.24)	#31
51 children	Paintings and furnishings in hospital wards	Increase symptoms of AD	Low pollutants rooms: SCORAD reduced from 42 ± 11.5 to 29.8 ± 8.9	#33
2536 children	Painting, floor covering and new furniture	Increased risk of allergic diseases and AD	Allergy: OR 1.8 (CI 1.3-2.6) Eczema: OR 1.9 (CI 1.4-2.7)	#34

Table 4. *Common VOCs emitting from paints.*

VOC classes	Molecules
Alcohols	3-octanol, isobutanol, 1,2-propandiol, Texanol, butanol
Aldehydes	Acetaldehyde, benzaldehyde, formaldehyde
Hydrocarbons - aromatic	Benzene, styrene, xylene, toluene, ethylbenzene, naphtalene, chlorobenzene
Hydrocarbons - aliphatic	Heptane, decane, undecane, haxane, nonane, dodecane
Esters	2,2,4 – trimethyl – 1,3-pentanediol monoisobutyrate, 2-(2- butoxyethoxy)-ethanol acetate
Glycols	Propylene glycols ethers (PEG), butyldiglycol
Biocides	5-chlor-2-methyl-4-isothiazolin-3-on (CIT), 2-methyl-4-isothiazolin-3-on (MIT)

Moulds

Moulds are frequent indoor air pollutants, in particular in popular buildings. Their presence can be related with health diseases, and it is a main cause for wall repainting.

Borchers *et al*. reported in their study (11) that moulds can be a cause of allergy and for asthmatics can potentially exacerbate their asthma. The moulds considered for “outdoors” were the *Alternaria* and the *Cladosporium*, those considered for “indoor” environment were the *Penicillium* and the *Aspergillus*.

A meta-analysis was conducted on studies regarding exposure to mould and moisture in homes in relation to asthma and allergy. Data was collected through questionnaires from eight cohorts of children born in Europe. The questionnaires from 31,742 children were analyzed and the results showed that exposure to visible mould and/or moisture during the first two years of life was associated with an increased risk of developing asthma in young children (0-2 years) and allergic rhinitis in children of school age (6-8 years) (12).

Another meta-analysis of observational studies with the aim to research the association between domestic mould, asthma and allergy in children, took into consideration 61 scientific publications. Visible moulds were associated with asthma, wheezing and allergic rhinitis (13).

A Cochrane review in 2015 regarded some studies dealing with the preventive effect of removing moisture and mould from private homes/schools/offices on airway symptoms, airway infections and asthma in adults and children. The authors have included 12 studies, affecting 8028 participants. They found moderate to very low-quality evidence that repairing mould-damaged houses and offices leads to a decrease of asthma-related symptoms and respiratory infections in adults compared to no intervention. The evidence that repairing schools did not significantly change respiratory symptoms in staff is very low-quality although pupils’ visits to physicians due to a common cold were less frequent after remediation of the school (14).

A review of 228 papers (37 out of them summarized in Tables) published in 2011, highlighted the environmental factors that can favor childhood asthma in industrialized countries. According to this analysis, the exposure to environmental tobacco smoke, living in homes close to busy roads, or in damp homes with visible moulds were found to be the most consistent factors associated with asthma in childhood (15).

Volatile Organic Compounds (VOCs)

In many studies, Volatile Organic Compounds, are reported as important components of painting, related to indoor air quality issues.

In Tasmanian, Australia, a study was carried out on a cohort of 962 children, of which 71.3% were males. The authors evaluated the impact of the environment where children used to sleep on the occurrence of asthma and/or wheezing when the children reached the age of 7, concluding that several environmental factors, including heating, painting walls, blankets and sheepskins, in addition to allergens, increase the risk of asthma.

In particular, it was observed an enhancement of the effect on wheezing within 12 months from the painting, probably due to the releasing of VOCs in the air. These data, which show the likelihood that in children allergic to house dust mites (HDM) VOCs could increase airway inflammation (16), confirm the results reported in three other publications cited by the authors (17-19).

A very detailed review of the effects of interior water-based paints on asthma was published in 2013 by a

group of London researchers (20). 13 epidemiological studies were analyzed, 11 in children and adolescents and two in adults, with a population ranging from 153 to 13,988 subjects depending on the study. Most of the studies were done in Europe, two in Australia, three in China and one in Japan. Two studies measured VOCs in houses in which the walls were recently painted revealing high values of organic solvents in air. High levels of aliphatic compounds (C8-C11) of 2,2,4-trimethyl 1,3-pentanediol diisobutyrate (TXIB) and butanol were also detected in recently repainted residences. A systematic review by Canova (21), on the effect of domestic paints on people with and without asthma symptoms demonstrated uncertainty about the effect of most VOCs as a cause or aggravating agent of asthma and underlined the importance the use of adequate ventilation during and after each new painting work and the importance that low-VOCs emission paints have to be developed and disseminated in Europe. In a relevant review of 2007 from Mendeel (10), in the 21 selected papers it was found out that organic chemical pollutant sources in household air could be multiple. In fact, aldehydes (formaldehyde), aromatic hydrocarbons (benzene, toluene, styrene, ethylbenzene, naphthalene, chlorobenzene, dichlorobenzene), aliphatic hydrocarbons (hexane, decane, nonane, undecane, dodecane), other VOCs such as trichloroethylene, tetrachloroethylene, limonene, and finally phthalate esters were detected in the domestic ambient air. Formaldehyde was considered the most important causative agent of possible effects on airway. Although modern water-based and solvent-based paints contain only a few of the substances mentioned above, newly painted walls have been reported in six publications as a risk factor for asthma exacerbation and lower airway irritation in both children and adults.

In a 2014 paper on exposure to VOCs related to asthma and allergy in children and adults, the authors reviewed 225 scientific publications. They reported that the most investigated VOCs classes are: total VOCs, aliphatic compounds, aromatic compounds, microbial and aldehydes, including the formaldehyde, which was the most studied substance. Overall, the evidence is insufficient to arrive at firm conclusions and new high quality and observational studies, as well as clinical trials, on exposure to domestic VOCs and their effects on asthma/allergy would be necessary in order to reduce exposure to VOCs of children and adults with asthma (5).

In 2015, a systematic review on VOCs and risk of asthma and allergy was done by a group of Anglo-American scholars. 53 studies were included in the review. Aromatics (*i.e.*, benzenes, toluene and xylenes) and formaldehyde were the main VOC classes studied, both in relation to the development and the exacerbations of asthma and allergy. Most of these studies had a high risk of "bias" and the review demonstrated that there is weak evidence that VOCs have a role in the development or exacerbation of asthma and allergic diseases in adults and children (22).

A study from South Korea has shown that painting the walls of 17 classes (affecting a total of 172 children) with low VOC content water-based paints did not aggravate asthma and allergic diseases of the children (9).

Polyethylene glycols (PEGs)

PEGs are widely used as co-solvent/additives in water-based paints, and it has been demonstrated that they have an effect on the endocrine system (reproductive system) in animal and in humans (20). However, further experimental models should be developed to clarify the mechanism by which VOCs act on the airways and reproductive and/or endocrine systems. In order to analyze the relationships between common chemicals detected at home and allergy risk, in a Swedish study modified ISAAC questionnaires were collected from the families of 10,851 children aged 1-5 years. Medical examinations and checks of the domestic environment were made in about 10% of the cohort through nursing staff and dust samples were collected from their homes to be analyzed. Of the various chemicals analyzed (aldehydes, alkanes, aromatic hydrocarbons, dimethyl alkanes, PEGs, methyl alkanes, organic acids and texanol), only PEGs were reported to increase the risk of asthma, rhinitis and eczema in a statistically significant way when present in ambient air (19).

Other studies on household air pollutants were focused on PEGs since these molecules appear to promote asthma, eczema and rhinitis in children. PEGs concentration in the ambient air depends on when the room has been painted and also on the cleaning of the house with water. These data were gathered in a Swedish work done on 390 preschoolers' homes and it was found that the

presence of humidity maintains the effect of the PEGs even months after the application of the paint (23).

Isothiazolinones

Isothiazolinones are used for antimicrobial effect in paints. In a 2014 European multicenter study, the authors assessed the amount of methylisothiazolinone (MIT) and related isothiazolinones. A total of 71 wall paints were bought randomly from different supermarkets across 5 European countries and MIT was found in 93% of the paints, with concentrations ranging from 0.7 to 180.9 ppm. The conclusion of the study was that the use of these substances is widespread in European countries. Greater control of these substances in paints is needed to prevent the allergic contact dermatitis they cause in workers (24) and, although the international rules have become increasingly restrictive on the use of these biocides, a more recent paper by the same authors highlighted that the presence of such toxic substances in paintings does not seem to be decreasing in Europe (25).

REPAINTING

Home interior painting has been associated with an increased risk of asthma in different studies (26-27). Asthma symptoms and respiratory infections were investigated by submitting a questionnaire on health to 462 students from 8 upper secondary schools in Malaysia while different pollutants were measured inside and outside the schools, finding a correlation between wheezing and recent indoor painting at home (26).

In another study, children with asthma exacerbation related to home paint exposure were screened using a cross sectional study design in which 163 children, coming from two general pediatric clinics, were included. Also in this case, the results demonstrated that home paint exposure is a significant risk factor of asthma attack (27).

Furthermore, in a recent study made in China on sleep disorders in children aged 3-14 years with and without allergic rhinitis were taken in account the characteristics of the interior environment. 427 children with allergic rhinitis and 1046 control children participated in the study and the outcome has been that emulsion paints and tobacco exposure in early childhood can be associated with hyperhidrosis during sleep (7).

Another research, which used ISAAC questionnaire, evaluated the risk of asthma and respiratory symptoms among 1056 students aged 12-15 years based on the air quality in their home and school environment. In particular, the results showed that the risk was significantly higher when the rooms of their house were recently repainted (28), an observation that is in accordance with the results reported in a previous review by Mendell M.J. (10).

INDOOR AIR QUALITY

A concept that is emerging is “Green buildings and Health”, *i.e.,* houses with high technology of heating and humidity control, located in places with respect for nature, where both indoor and outdoor paints play a fundamental role in maintaining air quality at levels appropriate to individual and public health (29). In a paper published in 2015, the correlations between “green homes” and the risk of asthma in children have been evaluated. In fact, using a questionnaire in a group of Boston families, the researchers have found that children of families living in “green homes” had less risk of asthma symptoms, less risk of asthmatic attacks and less absence from school due to asthma than children living in conventional houses (30).

ATOPIC DERMATITIS

Atopic dermatitis affects millions of people worldwide, often begins in early childhood and can persist into adolescence and adulthood. While the exact cause of this condition remains unclear, recent studies explored association between IAQ and AD.

A study evaluated the incidence of Atopic Dermatitis (AD) at 7 months of age in a cohort of children in Taiwan. 20,687 children had participated in the study. The analysis of the questionnaires distributed to parents demonstrated significant risk factors for the appearance of AD in children, in addition to parental atopy, related to renewal and new painting of the house during pregnancy (31).

A less substantial review analyzed if there is a correlation between allergic disease, air pollution and genetic predispositions. Authors have cited 94 papers (17 out of them were analyzed thoroughly) and, in particular among “indoor” pollutants, reported that VOCs could favor allergic and respiratory diseases by directing the immune system towards a Th-2 prevalence over the Th-1 function. These compounds have also been reported to facilitate Atopic Dermatitis (32).

A 2011 CBA controlled study in Korea has involved 51 children, with a mean age of 1.7 years, looking for an

association between Atopic Dermatitis symptoms and air quality. The authors created a low-pollution environment in the hospital: the rooms were built and decorated (paintings and furnishings) with low-pollution material, an air curtain was installed above the entrance and an air purifier-ventilator was put in the room. Patients were kept in this environment for an average of 3.3 days. Air quality was assessed every week by measuring: PM 2.5 and PM 10, formaldehyde, TVOC (benzene, toluene, ethylbenzene, xylene and styrene), CO, CO_2, NO_2, suspended bacteria and environmental mould. The quality of the ambient air was also evaluated in the rooms of the houses of each patient. In patients' home rooms the environmental factors studied were significantly higher in concentration than in the low-pollution hospital rooms, with the exception of benzene, toluene, ethylbenzene, xylene, CO and NO_2. The health of children improved during the days elapsed in the hospital and, when these children have been returned at home, 22 of them maintained the improvement regarding skin symptoms while the other 29 worsened. Among this group, the bedrooms of 2 children were newly repainted and for another 2 children wrapping paper was put on the walls. Moreover, 8 children among the group with worsened Atopic Dermatitis symptoms were hospitalised again, and consequently their health has improved again. This study has therefore shown that by placing children with AD in the appropriate home environment their health can improve (33).

Other authors reported similar results. Within an epidemiological study involving 2536 children exposed to paintings, floor coverings and new furniture before birth and in their first year of life, it has been found that the redecoration is related to allergic symptoms and 1.9 eczema (34).

A paper published in JACI has given an interesting interpretation on the onset of food allergy in children, which would depend on both skin barrier mutations and co-stimulating environmental factors (35). In this paper, researchers studied an experimental model in mice with mutation for filaggrin (analogous to the mutation studied in children with AD). These new-born mice were sensitized through the skin with food and environmental allergens such as Alternaria and Mites. In this way began the stimulation Th-2 that led to the AD and the anaphylactic reaction when the food was also introduced by mouth (and this in a more striking way in children of allergic mothers). On the other hand, when food was introduced by mouth before environmental skin sensitization, the anaphylactic reaction no longer appeared. This experimental study demonstrated the importance of two factors in inducing food allergy with skin manifestations (AD) or anaphylaxis: congenital skin barrier defect and stimulating environmental factors (food proteins, mites, Alternaria) (35). More studies are needed to demonstrate if the indoor pollutants reported in previous papers (31, 33, 34) could play a similar role.

PROACTIVE INITIATIVES TO REDUCE THE RISKS FROM AIR POLLUTION

Indoor air pollutants can cause many harmful effects. While further research is needed, understanding, and controlling common pollutants can help reduce the risk of indoor health concerns. Considering the potential risks of such substances also in the health of the fetus and infant, it is imperative that government agencies and organizations implement proactive measures to prevent potential adverse health outcomes. Today in many countries certifications exist to define Indoor Air Quality.

The Environmental Protection Agency (EPA), the executive agency tasked with environmental protection matters in the US, defines environmental justice (EJ) as "the fair treatment and meaningful involvement of all people (…) with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies" (37).

EPA's Indoor Environments Division (IED) provides guidance and programs to help build the capacity of communities to understand and avoid indoor and outdoor health impacts.

European countries on the other hand are trying to tackle some of the sources of indoor air pollution by restricting the use of toxic substances or finding ways to reduce emissions. In Europe are emerging more and more restrictive requirements, both governmental and voluntary (**Table 5**). These requirements promote the development of low VOCs emitting paintings and are directly accepted as proof from programs for sustainable buildings.

Nevertheless, promoting new laws on this topic is not the only way to improve the quality of the air, but it is also necessary to increase perception in people, manufacturers, and builders on IAQ topics.

***Table 5**. Most relevant certifications regarding indoor air quality for paints and construction.*

Certification	Country/Institution	Application	Type	Ref.
Emission Level	France	Painting products	Compulsory	#39
CAM	Italy	Construction specification	Compulsory for public procurements	#40
Indoor airPLUS	EPA (USA)	Construction specification	Voluntary	#41
AgBB – ABG	Germany	Products for indoor use	Compulsory	#42
BREEAM	Building Research Establishment	Construction specification	Voluntary	#43
LEED	U. S. Green Building Council	Construction specification	Voluntary	#44

CONCLUSIONS

The Total Exposure Assessment Methodology (TEAM) Study of Environment Protection Agency in US has found levels of about dozen common organic pollutant to be 2 to 5 times higher inside homes than outside (38). VOCs and fine particles can play a role in allergy and respiratory diseases in children and in part they are due to the wall paints.

More studies are needed to explore the correlation between emissions resulting from painting walls and the possible effects on respiratory and allergic diseases in children (8) and taking in account the presence on the market of products with low VOCs, it is necessary to analyze the correlation between VOCs concentration in the paint with respiratory diseases.

In many cases the evidence is insufficient to arrive at firm conclusions therefore new high quality and observational studies, as well as clinical trials, on exposure to domestic VOCs and their effects on asthma/allergy would be necessary, despite the difficulties to find funds, participants, and to measure changes in indoor air composition and well-defined outcomes. A lot of work still remains to be done by color manufactures and wall paint industries to identify which chemicals have to be used more safely in the living environment of children, in order to reduce exposure to VOCs of children and adults with asthma and allergy.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Conceptualization, draft, supervision: AB, GM. Check international medical databases: AB. Writing, tables, figures, review: AB, BZ, GM.

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Human studies and subjects

N/A.

Animal studies

N/A.

Data sharing and data accessibility

The data underlying this article are available in the article.

Publication ethics

Plagiarism

This is a review article and all original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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CASE REPORT

Impact of mood disorders in a pediatric patient with severe asthma

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ABSTRACT

Asthmatic children may be more likely to develop psychiatric disorders, including depression and anxiety, that may negatively influence the management and the degree of asthma control. We describe the case of a 15-year-old girl admitted to our Pediatric Unit for post-infectious severe asthma.
The first psychological evaluation showed an unsettled mood. Treatment with Long-Acting Beta2-Agonists (LABA)/Inhaled Corticosteroids (ICS) high dosage and anti-leukotriene was prescribed, and gradually suspended over three months without exacerbations. Psychological interviews were also performed. After a three-months follow-up, psychological tests showed a serene mood and no depression or anxiety symptoms. The resolution of depressive-anxious symptoms through psychotherapy may result in clinical improvement even in the absence of therapy for asthma, suggesting that psychological evaluation is crucial to improve the control of the disease. A close collaboration between mental health professionals and allergists could result in improved symptoms control, quality of life, overall functioning and, ultimately, decreased mortality.

IMPACT STATEMENT: A single-center experience about the role of psychotherapy and psychological tests in the management of patients with asthma.

INTRODUCTION

Asthma is the most common chronic inflammatory airway disease, significantly impacting the quality of life of children and their families (1). Asthmatic children may be more likely to develop psychiatric disorders, including depression and anxiety, that may negatively influence the degree of asthma control (2). Psychological evaluation with the administration of appropriate tests to the asthmatic patient may be helpful in the management of the disease (3). Herein, we describe the case of a patient with severe asthma who benefited from psychotherapy.

CASE PRESENTATION

A. is a 15-year-old girl admitted to our Pediatric Unit for fever and cough with dyspnea. The primary care physician prescribed oral systemic corticosteroids (OSC, betamethasone 1 mg/day), without benefit. Her clinical history was positive for obesity. She experienced episodes of wheezing, dyspnea following exercise, and bronchospasm. She did not practice any sports. Her parents were smokers.

KEY WORDS
Asthma; children; case report; mood disorders; psychotherapy.

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She reported having pets at home. At the admission, general clinical conditions and vital signs were normal. On physical examination, her weight was 116 kg (+2.75 SD), height 169 cm (+1.12 SD), and Body Mass Index (BMI) 40.61 kg/m^2 (+3.39 SD). She was neglected in clothing and disinterested in social life. She also presented acanthosis nigricans in interdigital, neck and inguinal folds, pearly streaks on the abdomen and reduction of the air penetration at the thoracic auscultation, with moans and whistles. Arterial hemogasanalysis was performed: pH 7.41, pCO2 30.3 mmHg, pO2 98 mmHg, BE -1.6 mmol/l, HCO3- 23.6 mmol/l. Paper RadioImmunoSorbent Test (PRIST) and Radio Allergo Sorbent Test (RAST) documented serum total IgE levels >3000 kU/, and positivity of specific IgE for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Parietaria judaica*, *Felis domesticus* and *Canis familiaris*. Cardiological evaluation and chest X-Ray (**Figure 1**) were normal; chest Computer Tomography (CT), performed because of the persistence of reduction of the air penetration at the thoracic auscultation despite antibiotic treatment, was also negative (**Figure 2**).

A psychological interview was performed to examine her emotions and cognitions, highlighting a non-serene mode tone. Laboratory tests showed neutrophilic leukocytosis (White Blood Cells 11000/mmc, Neutrophils 9460/mmc) and elevation of C-Reactive Protein (3 x N). Serum *Mycoplasma pneumoniae* IgM levels were positive; thus, antibiotic therapy with macrolides was started. Treatment with OSC (prednisone 50 mg/day) and Short-Acting Beta2-Agonists (SABA) was also administered and modulated according to the clinical course. After discontinuing therapy, spirometry with a bronchodilator (BD) reversibility test was performed (pre-BD FEV1 3.52 L *vs.* post-BD FEV1 4.01 L; pre-BD FVC 4.00 L *vs.* post-BD FVC 4.02; pre-BD FEV1/FVC 88% *vs.* post-BD FEV1/FVC 100 ~ +12%) (**Table 1**). On the 10th day, she was discharged and treatment with anti-leukotriene (10 mg/day), Long-Acting Beta2-Agonists (LABA, 100 ug/day) and Inhaled Corticosteroids (ICS, 500 ug/day) was prescribed at home. Psychotherapy was also started. Over 3 months of follow-up, no asthma flare-ups were reported; thus, LABA/ICS treatment was decreased and replaced with ICS (250 ug/day), while therapy with anti-leukotriene was suspended. In parallel, psychological tests (Raven Standard Progressive Matrices (4), Emotional Quotient Inventory Youth Version (5), Multidimensional Anxiety Scale for Children (6), Multidimensional Self Concept Scale (7)) detected a serene mode-tone, no behavioral disorders with no evidence of anxious or depressive mood.

Table 1. *Spirometric values.*

	pre-BD	post-BD
FEV1 (L)	3.52	4.01
FVC (L)	4.00	4.02
FEV1/FVC (%)	88	~100 (+12)

DISCUSSION

Asthma is the most common airway disease in the pediatric age, characterized by chronic inflammation and airway hyper-reactivity leading to cough, wheezing, difficulty in breathing, and chest tightness (1). The patho-

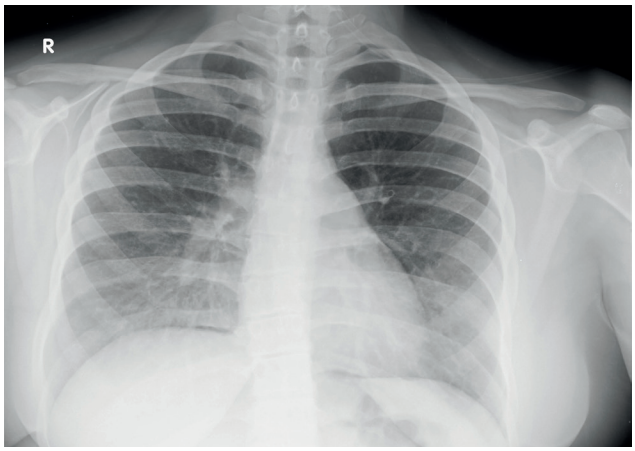

Figure 1. *Anteroposterior X-Ray of the chest.*

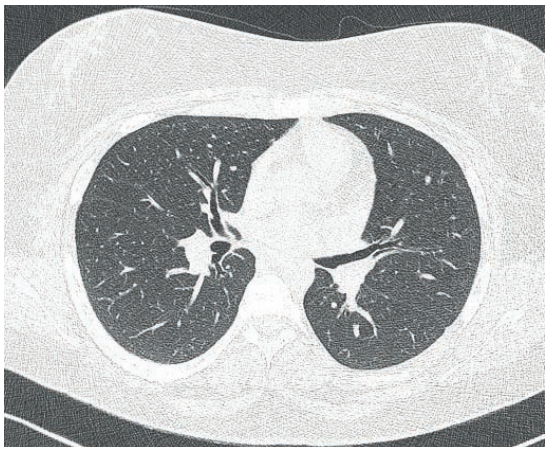

Figure 2. *Chest Computer Tomography (CT) cross section.*

physiology of asthma is complex, and bronchial hyperreactivity, inflammatory cell infiltration, release of several chemical mediators and airways structural remodeling are involved in the asthma onset (1). It is estimated that more than 300 million people worldwide are affected by asthma (8). While asthma prevails in the male sex during childhood, female subjects are most affected since adolescence (8). 5% of asthmatic patients experience a severe phenotype featured by frequent exacerbation, need for hospitalization, complications, and poor quality of life with a significant psychosocial impact (9, 10). Several analyses show the connection between mood disorders and asthma. Several causal pathways explaining the relationships between depression, risk behavior, non-adherence to treatment, and symptoms control in young people with asthma have been proposed (11). Suffering caused by the inadequately controlled disease may result in psychological disorders; depression may increase asthma symptoms through poor self-management of the disease and induce physiological changes, which, in turn, increase airway inflammation, mediated by IL-6, IL-9, and IL-13 release. Genetic predisposition to mood disorders and asthma can also significantly impact this link. Accordingly, patients with mood disorders require psychological intervention, without which any mood, behavior, or asthma control improvement is unlikely. Depression, family conflict, and non-adherence to treatment may be lethal for children and adolescents with asthma. Strunk *et al*. (12), evaluating the circumstances surrounding asthma death in children and adolescents, examined the cases of 21 patients who later died of asthma with a stepwise discriminant analysis to assess the predictive role of 57 physiological and psychological variables. The emerging risk profile of asthma death included families with histories of conflict between parents and adolescents, depressive symptoms in children and adolescent patients, family dysfunction, such as parental psychopathology or alcoholism, ignoring asthma symptoms, poor self-care, and adherence. Bender and Zhang (13) evaluated how psychological status may influence asthma control in 104 subjects, aged 6 to 18 years, through questionnaires completed separately by children and parents to assess asthma symptoms and mood disorders (anxiety and depression). Contextually, adherence to therapy was assessed through electronic devices attached to inhalers. Higher negative affective scores were associated with more frequent symptoms. High anxiety and depression scores were significant predictors of absences from school. One potential explanation of the relationship between negative affective states and asthma symptoms could be found in poor treatment adherence in response to mood disorders, resulting in decreased disease control. To test this possibility, authors evaluated the relationship between therapy adherence and symptom control and objective health events (peak prednisone use, school absences, and emergency room visits). Results showed that adherence was not significantly associated with either symptom reported by children or parents. Non-adherence was associated with increased CS use. In summary, non-adherence predicted CS use but not subjective symptoms. Kulikova *et al*. (3) suggested that anxiety and depressive symptoms may be associated with worsened asthma outcomes, such as asthma control and quality of life. Anxiety emerged as the most important predictor of poor asthma outcomes, particularly in girls, suggesting that girls may perceive asthma more negatively than boys and be more anxious about the disease. Anxiety also may affect daily quality of life, worsening the perception of asthma symptoms and increasing the emotional burden associated with it. These findings suggest that it may be essential to screen asthmatic children and adolescents for depressive and anxiety symptoms, as well as assess the asthma-related quality of life in structured formats, as part of routine asthma management. Recently, Plaza-González *et al*. (2) highlighted that asthma is a disease with a psychosomatic basis, so negative psychological and sociocultural factors may negatively influence the quality of life of pediatric asthmatic patients. Children with asthma are more often obese or overweight, they have impaired immune systems and sleep quality, and their health is further compromised if they are bullied or harassed at school. Asthmatic children generally perform worse academically and have lower socioeconomic status than healthy children. Dysfunctional family and social relationships in asthmatic children negatively influence asthma management and quality of life, so it is important to identify these risk factors and psychological comorbidities, aiming to achieve a better control of the disease. Treatment options may include cognitive behavioral therapy, psychoeducation, relaxation, drug treatment and biofeedback (14).

In conclusion, a psychological evaluation may be necessary to improve asthma control; the resolution of depressive-anxious symptoms through psychotherapy may result in clinical improvement even in the absence of asthma therapy, particularly among a specific cluster of patients with associated risk factors.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Author contributions

FF, FM and SFR wrote the manuscript. MP contributed to the discussion. GC and SC collected the references. SM and LC reviewed the manuscript. Each Author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. All the Authors read and approved the final manuscript.

Ethical approval

Human studies and subjects

The manuscript was written according to Good Clinical Practice and in compliance with the Declaration of Helsinki with successive amendments.

Animal studies

N/A.

Data sharing and data accessibility

The data underlying this article can be shared just before a reasonable request to the Corresponding Author.

Publication ethics

Plagiarism

The contents of the article are original and any overlaps with other articles are by the Authors themselves and appropriately cited.

Data falsification and fabrication

All the data correspond to the real.

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CASE REPORT

Surfactant dysfunction and neurodevelopmental delay: a new ABCA3 mutation

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ABSTRACT

ABCA3 is a transmembrane protein found on the limiting membrane of lamellar bodies of alveolar type II cells. Its role is the transport of phospholipids for surfactant production. Over 200 ABCA3 mutations are known to compromise ABCA3 functions and bring to different phenotypes, from neonatal respiratory distress syndrome to childhood or adult diffuse interstitial lung diseases.

We report the case of a19-month-old girl, born at term age, developing respiratory distress six hours after birth. During the first months of life, she developed recurrent long-lasting and oxygen-dependent lower respiratory tract infections, failure to thrive and neurodevelopmental delay. Because a surfactant deficiency was hypothesized, the four genes responsible for primary surfactant dysfunction were analyzed by Next Generation Sequencing. Two mutations were found in the ABCA3 gene (c.2888A > G and c.4714C > T), one inherited from each parent.

To our knowledge, there is no previous reporting of correlation between ABCA3 mutation and neurodevelopmental delay. Neurological abnormalities are instead related to another surfactant dysfunction, caused by NKX2-1gene mutation. Further cases and accurate genetic diagnosis could be useful to validate this new correlation.

IMPACT STATEMENT: ABCA3 is correlated to surfactant dysfunction and respiratory diseases. We present a case report in which surfactant dysfunction combines to mild neurodevelopmental delay, in a patient carrier of compound heterozygosity never described before on ABCA3 gene (c.2888A>G and c.4714C>T).

CASE REPORT

C.C. is a19-month-old girl with recurrent respiratory distress due to long-lasting and oxygen-dependent lower respiratory tract infections, failure to thrive and neurodevelopmental delay.

She is a female twin born at 38 weeks of gestational age by elective caesarean delivery in dichorionic diamniotic twin pregnancy. Neither consanguinity nor other relevant illnesses were reported in her family history. Apgar score was 10-10. Weight (2900 gr) and length (48 cm) were appropriate for gestational age. Six hours after birth the infant developed RDS, initially managed with continuous positive airway pressure. Because of neonatal RDS stage II-III at chest x-rays, surfactant was administered. On day two after birth, clinical conditions got worse,

KEY WORDS
ABCA3 mutations; surfactant dysfunction; neurodevelopmental delay; case report.

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and the baby was intubated. The patient was extubated after 6 days, and oxygen support was suspended only after 33 days.

The baby also presented hypotonia and neurodevelopmental delay from birth, with no anomalies at cranial ultrasound. Neurodevelopmental delay was confirmed in the next months. She reached sitting position at 12 months, with no capacity of quadruped and crawling at 13-months-old and poor lallation. Brain MRI performed at 13 months was normal. So CGH-array (Comparative Genomic Hybridization Array) was performed and two variants of uncertain significance – maybe related to restless leg syndrome – were found. Now, at 19-months-old, she is not able to stand and walk and the lallation is still strictly poor.

She suffered for lower respiratory tract infections and required six hospitalizations for respiratory support. Even without acute infection, the patient presented polypnea with 30 to 50 breaths per minute respiratory rate, mild subcostal retractions and 93 to 95% peripheral oxygen saturation. The chest x-rays and chest ultrasounds always showed interstitial lung pattern on upper lobes and even peribronchial consolidation with air-trapping. The chest tomography (executed at 15-month-old during a long-lasting infection) showed ground glass opacities and parenchymal consolidations (**Figure 1**).

During hospitalization, she was administered antibiotics, systemic and inhaled corticosteroids, and oxygen support (mainly through high-flow nasal cannula). Multiple investigations were performed (all unremarkable): cystic fibrosis genes mutations, alpha-1 antitrypsin level, lymphocyte typing, immunoglobulin and thyroid hormones levels, transglutaminase Ab, hemogasanalysis, lactate-to-pyruvate ratio, stool elastase. Because of failure to thrive milk protein free diet was started twice, at 3 months and 15 months, with partial response (**Figure 2**).

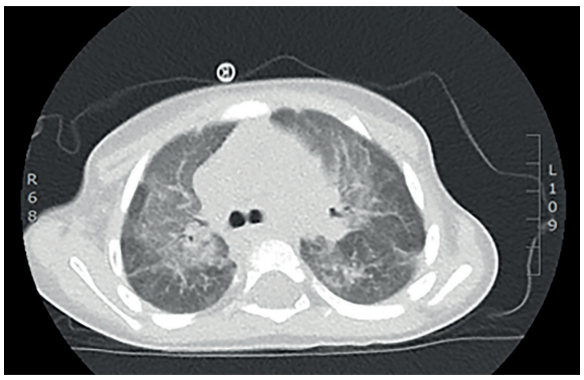

***Figure 1**. Chest tomography at 15 months.*

At the end we required blood DNA analysis of four genes by Next Generation Sequencing (SFTPC, SFTPB, NKX2-1, ABCA3), because a genetic surfactant deficiency was supposed. The analysis revealed in trans compound heterozygosity for ABCA3 mutations: c.2888A>G on exon 21, inherited from mother and c.4714C>T on exon 30, inherited from father. No mutation was found in other surfactant protein genes (SFTPC, SFTPB, NKX2-1).

After diagnosis, she started steroid therapy with prednisone 1 mg/kg, with good clinical response and reduction of hospitalization for lower tract respiratory infections.

DISCUSSION

ABCA3 gene mutations have been associated with RDS and pediatric ILD (5, 6). Correlation between genotype and phenotype is already known. Patients with null/null mutations have poor prognosis: generally, they present RDS at birth and die or undergo lung transplantation before 1 year of age. The outcome of subjects with null/other and other/other genotypes is more challenging (7). The most common ABCA3 mutation is p.Glu292Val (or p.E292V, c.875 A>T)(5, 8, 9). To our knowledge this is the first time these mutations have been reported. Flamein *et al*. reported that the c.2888A>G mutation on a single allele is related to death for neonatal RDS (10). In NHLBI Exome Variant Server c.288A>G mutation is not reported, while c.4714C>T mutation is reported as a coding-synonymous mutation. COSMIC (Catalogue Of Somatic Mutations In Cancer) reported c.4714C>T mutation as pathogenic (score 0.91 FATHMM prediction).

Since our patient presented ILD, poor growth could be explained by increased energy consumption due to increased respiratory work and recurrent infections. Cow's milk free diet was prescribed twice, with decent weight gain, but persistence of lower respiratory tract infections. Hence, Heiner syndrome was excluded (11). She also presented neurodevelopmental delay. To our knowledge, there's no evidence about ABCA3 compound heterozygous mutations related to neurological problems.

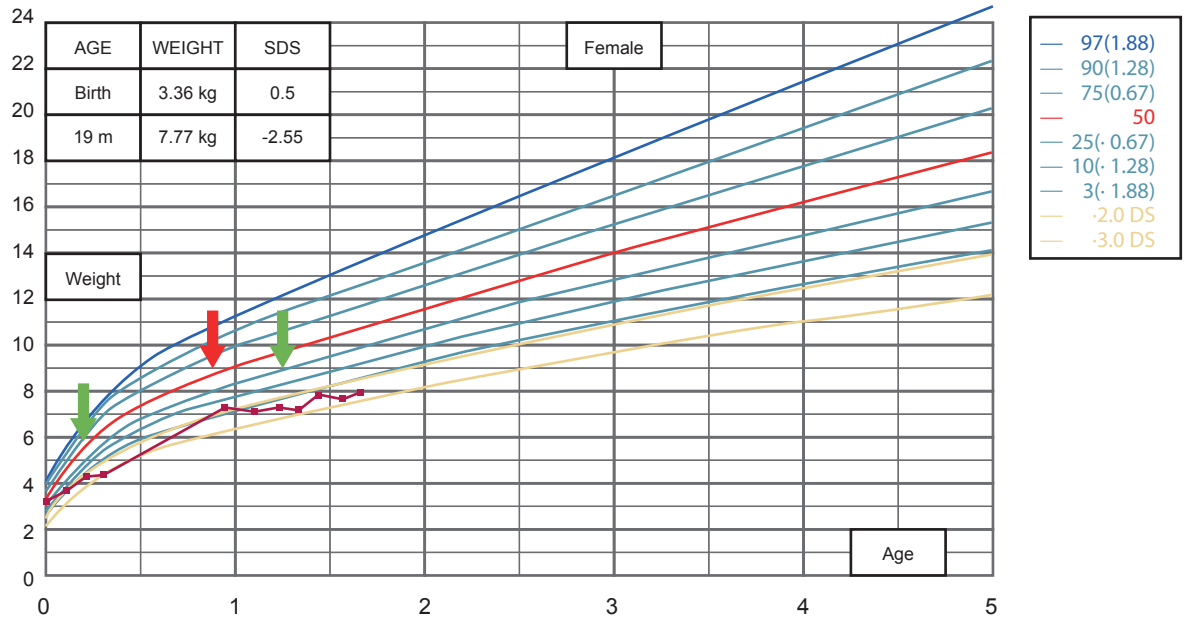

***Figure 2**. WHO child growth standard. Failure to thrive, from 0.5 SDS of birth, to -2.55 SDS now. Green arrows show the begin of cow-milk-protein free diet, red arrow the suspension. Data are expressed in kg and in years for age. SIEDP Growth Calculator Application.*

Neurodevelopmental delay and muscular atrophy were described by El Boustany *et al*. in a girl with severe respiratory failure after 4 years of mechanical ventilation through tracheostomy (12). Si *et al*. observed developmental delay of varying severity and poor weight gain in three patients with ABCA3 mutations and they related it to probable chronic illness sequelae (13). Neurological abnormalities and surfactant dysfunction are related when the mutation is on NKX2-1 gene, encoding thyroid transcription factor, resulting in the brain-thyroid-lung syndrome (14-16).

CONCLUSIONS

Over 200 ABCA3 mutations have been found and related to surfactant dysfunction, leading to a wide clinical spectrum, from neonatal RDS to adult ILD. Our patient, with a compound heterozygosity for ABCA3 mutations in trans, presented a new phenotype not previously described, characterized by not only lung disease but also important failure to thrive and neurodevelopmental delay. To our knowledge, the correlation between ABCA3 mutation and neurodevelopmental delay hasn't been described yet. Further cases and accurate genetic diagnosis could be useful to validate this new correlation.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Author contributions

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Ethical approval

Human studies and subjects

N/A.

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N/A.

Data sharing and data accessibility

The data underlying this article are available in the article.

Publication ethics

Plagiarism

The contents of the article are original and any overlaps with other articles are by the Authors themselves and appropriately cited.

Data falsification and fabrication

All the data correspond to the real.

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