



Research papers

Bronchocele density in cystic fibrosis as an indicator of allergic broncho-pulmonary aspergillosis: A preliminary study



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ABSTRACT

Objective: Allergic broncho-pulmonary aspergillosis (ABPA) is a severe and under-diagnosed complication of cystic fibrosis (CF). The aim of the study was to determine whether the mucus content of bronchoceles in cystic fibrosis complicated with ABPA reveals a higher density than the mucus content of non-ABPA cystic fibrosis.

Materials and methods: We studied retrospectively 43 computed tomography scans (CT scans) of a pediatric population of cystic fibrosis patients. We measured the mucus attenuation in Hounsfield Units (HU) of all bronchoceles > 5 mm in diameter.

Results: We found bronchoceles > 5 mm in 13/43 patients. 5/13 patients had a positive diagnosis of ABPA. The median HU value of bronchoceles was higher in patients with than without ABPA [98 HU (26–135) vs 28 HU (10–36); $P = 0.02$]. Moreover, all patients with a bronchocele density > 36HU were ABPA positive.

Conclusions: CF complicated with ABPA shows higher attenuation bronchoceles on CT scans of the chest. Systematic density measurements of bronchoceles could help to raise the difficult diagnosis of ABPA in patients suffering from cystic fibrosis. Larger series could confirm a threshold in HU which could become a new imaging criterion for the diagnosis of ABPA.

1. Introduction

Cystic fibrosis (CF) is the most common lethal inherited disease in Caucasians. The disease occurs in 1 in 2500–3500 newborns in Europe and United States. It is an autosomal recessive disease, caused by mutations to the cystic fibrosis transmembrane conductance regulator (CFTR) gene [1]. The CFTR protein plays a vital role in transporting salt and water across the surface of epithelia. The abnormal function of this protein affects many organs of the body, especially the lung epithelia leading to the production of thick, sticky mucus which results in chronic lung infection and inflammation [2]. Pulmonary involvement is the major cause of mortality and morbidity of CF.

Allergic broncho-pulmonary aspergillosis (ABPA) is a disease condition characterized by chronic airway inflammation and airway damage resulting from persistent colonization by and sensitization to the

fungus *Aspergillus fumigatus* [3]. In CF, it commonly complicates the clinical course of patients and can cause rapid progression of bronchiectasis and fibrosis [4–6]. Thus, earlier recognition of ABPA improves patients prognosis and delays the development of bronchiectasis, one of the manifestations of permanent lung damage in CF [7].

ABPA often manifests in late childhood in CF, the rates in pediatric population varies from a less than 1% (Serbia) to 18.6% (Switzerland) [8]. This variability is partly explained by the diagnostic difficulty due to overlapping clinical, radiological, and biological findings occurring in ABPA and CF [9]. A recent large multicountry study with review of the literature has shown that ABPA diagnosis delay could reach 10 years after the beginning of the symptoms, and the same study suggests that depending on the countries, as much as 50% of ABPA cases could be underdiagnosed [8]. So far, radiological signs of ABPA are utterly unspecific: the classical bronchiectasis, mucus plugging, lung infiltrates

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ABPA, allergic broncho-pulmonary aspergillosis; CT-scan, computed tomography scan; HAM, high attenuation mucus; HU, hounsfield units; ROI, region of interest; MDT, multidisciplinary meeting; IQR, interquartile range; CI, confidence interval; ROC, receiving operating characteristic; MRI, magnetic-resonance imaging; WW, window width; WL, window level

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and branching nodules proposed at the last cystic fibrosis consensus conference [10] are seen in most patients suffering from cystic fibrosis, whether they are complicated with ABPA or not. To pinpoint a new specific imaging feature could prove very useful to support the positive diagnosis and reduce diagnosis delay of ABPA.

ABPA also occurs in adults with recurrent asthma, and in this population, high attenuation mucus (HAM) is a characteristic radiologic finding suggesting the diagnosis with high specificity levels [11,12].

Whereas the mucus plugs commonly seen in CF are described as low-attenuation density [13], to our knowledge, the possible variations of mucus density and higher attenuation of bronchoceles in cystic fibrosis complicated by ABPA has never been studied before. The literature mentions only one case-report of a child with cystic fibrosis presenting a high attenuation mucus plugging caused by ABPA [13].

The aim of our study was to determine whether the mucus content of bronchoceles in cystic fibrosis complicated with ABPA shows a higher density content than the mucus content of non-ABPA cystic fibrosis.

2. Materials and methods

We studied retrospectively the chest computed tomography scans (CT-scans) of a pediatric population of cystic fibrosis patients performed between May 2013 and June 2015 in Nice Pediatric University Hospital. The indication was either routine follow-up CT scan (Table 3, column 2 note as –) or clinical pulmonary deterioration (Table 3, column 2 note as +).

A CT-scan of the chest was performed on 16-detector row multi-detector CT scanner (BrightSpeed Elite Velocity General Electric) with a 512 matrix size. The images were evaluated on lung window: window width (WW) of 1600 Hounsfield units (HU) and window level (WL) of – 400 HU and on mediastinal window: WW of 400 HU and WL of 40 HU.

The CT-scans were obtained in supine position at end inspiration from the lung apices to the bases. The images (1.25 thickness at 10-mm intervals) were reconstructed using the high-spatial frequency algorithm. Image analysis was performed independently by a 10-years' experience chest radiologist and a 3-years' experience pediatric radiologist both blinded to the final diagnosis.

We included patients showing bronchoceles accordingly to the Fleischner Society [14]: a bronchocele is bronchial dilatation due to retained secretions (mucoid impaction) appearing on CT scan as a tubular or branching Y- or V-shaped structure that may resemble a gloved finger. We chose arbitrarily a transverse diameter greater than 5 mm in order to have a significant region of interest (ROI); below this size the ROI area could not be properly applied.

We measured the mucus attenuation in HU, with a round or elliptic ROI placed near the center of the mucoid impaction, when possible far from the bronchial wall.

In patients showing multiple bronchoceles, we recorded the density of each bronchocele but only the highest density was used for the statistical analysis.

Bronchoceles blurred by movement artefacts due to cardiac or respiratory mobility were excluded from the study.

ABPA was diagnosed according to the Cystic Fibrosis Foundation Consensus Conference [10] in multidisciplinary meeting (MDT) (Table 1), the members of the MDT were blinded to bronchocele density scores.

We compared the density of bronchoceles in HU with the diagnosis of ABPA.

2.1. Statistical analysis

Continuous variables were reported as mean with standard deviation and median with interquartile range (IQR), while categorical variables were reported with proportions and percentages. Univariate

Table 1

Minimal diagnosis criteria of ABPA according to the Cystic Fibrosis Foundation Consensus Conference.

All of following major criteria :
I. Acute or subacute clinical deterioration with no other cause.
II. Total serum IgE > 500 IU/ml.
III. Cutaneous hypersensitivity to <i>Aspergillus</i> or in vitro demonstration of IgE antibody to <i>Aspergillus</i> .
And one of the following minor criteria:
I. Precipitating <i>Aspergillus</i> antibodies or in vitro demonstration of IgE antibody to <i>Aspergillus</i> .
II. Radiographic changes such as infiltrates, mucus plugs or bronchiectasis that have not resolved with antibiotic and physical therapy.

analysis using the Mann–Whitney *U*-test was performed to compare densities of bronchoceles in patients with and without ABPA. A P-value of less than 0.05 was considered statistically significant. Intraclass correlation coefficient (with corresponding 95% Confidence Interval (CI)) of bronchoceles density measurements between the readers was calculated to evaluate their reliability (for both absolute agreement and consistency). Statistical analysis was performed using Medcalc software (Version 14.12.0, Ostend, Belgium).

3. Results

We reviewed CT scans of 43 cystic fibrosis patients: 13 patients (4–19 yo, mean 12.5 yo) were included in the study, presenting with bronchoceles > 5 mm (Tables 2 and 3).

11 CT-scans were performed without intravenous (IV) contrast and 2 CT-scans were IV enhanced.

The delay between the CT scan and the biologic tests leading to the diagnosis of ABPA was less than 3 weeks except in one case (6 weeks).

Correlation between the two reader measures was excellent, with intra-class coefficient (95% CI) of 0.946 (0.813–0.984) for absolute agreement and 0.956 (0.863–0.986) for consistency.

The density measurements of bronchoceles ranged from 10 to 135 HU with a median at 31 HU and a mean at 49 HU.

5/13 patients had a positive diagnosis of ABPA with density measurements of bronchoceles ranging from 26 HU to 135 HU (median 98 HU, IQR [41–123]) (Fig. 1).

8/13 patients were not ABPA, the density measurements in this population ranged from 10 to 36 HU (median 28 HU, IQR [23–32.5]) (Fig. 2).

The median of the density of the bronchoceles differed significantly between ABPA positive and ABPA negative patients, respectively 98 HU and 28 HU ($P = 0.02$).

In this series, all patients with bronchocele density > 36HU were ABPA positive.

Table 2
Results.

Patient	Age (Year)	Density of bronchoceles HU		
		Radiologist 1	Radiologist 2	ABPA
1	10	21	12	–
2	14	46	47	+
3	14	34	30	–
4	10	30	25	–
5	16	31	28	–
6	4	120	119	+
7	14	26	21	–
8	15	26	28	+
9	15	98	95	+
10	19	25	15	–
11	13	10	12	–
12	10	135	93	+
13	8	36	31	–

Table 3

Clinical-biological data.

Patient	Clinical deterioration	IgE total	IgE antibody to <i>Aspergillus</i>	Precipitating <i>Aspergillus</i> antibodies	Multidisciplinary meeting final diagnosis
1	+	103	4	–	Acute bronchopneumonia
2	+	1636	61	+	ABPA
3	+	17	< 0.1	–	Acute bronchopneumonia
4	+	15	< 0.1	–	Acute bronchopneumonia
5	+	9	< 0.1	–	Acute bronchopneumonia
6	+	1027	16	–	ABPA
7	–	22	0.23	–	No disease progression
8	+	833	10	+	ABPA
9	+	1387	16	+	ABPA
10	–	304	7	–	No disease progression
11	+	741	14	–	Necrotizing pneumonia
12	+	3981	55	+	ABPA
13	–	13	< 0.1	–	No disease progression

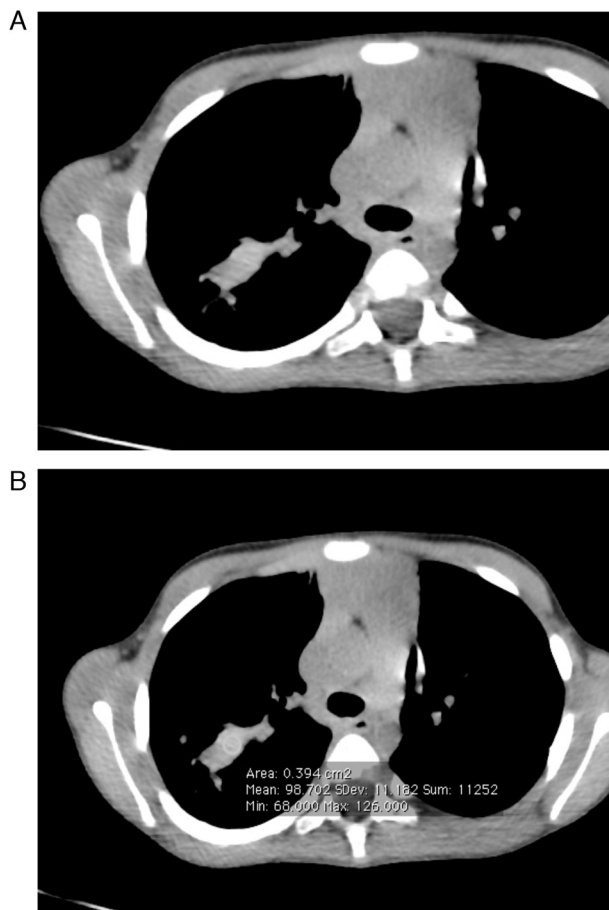


Fig. 1. Axial CT image of the chest on mediastinal window: patient 6, ABPA +. A. Posterior segment of right upper lobe central bronchocele, B. High-attenuation bronchocele: ROI, mean HU = 98.702

4. Discussion

Results of our study suggest that CF complicated with ABPA tends to show higher attenuation bronchoceles on chest CT scan whereas non-ABPA CF shows low-attenuation bronchoceles, as described in the literature [13]; in our series, all patients with a bronchocele density > 36 HU had a positive diagnosis of ABPA, and only one patient with ABPA showed a low density content of its bronchocele.

ABPA is a frequent complication that occurs in two categories of patients: asthmatic and cystic fibrosis patients. It causes significant respiratory symptoms in particular when the diagnosis is delayed. The prevalence of ABPA ranges from 1 to 19% in patients with cystic

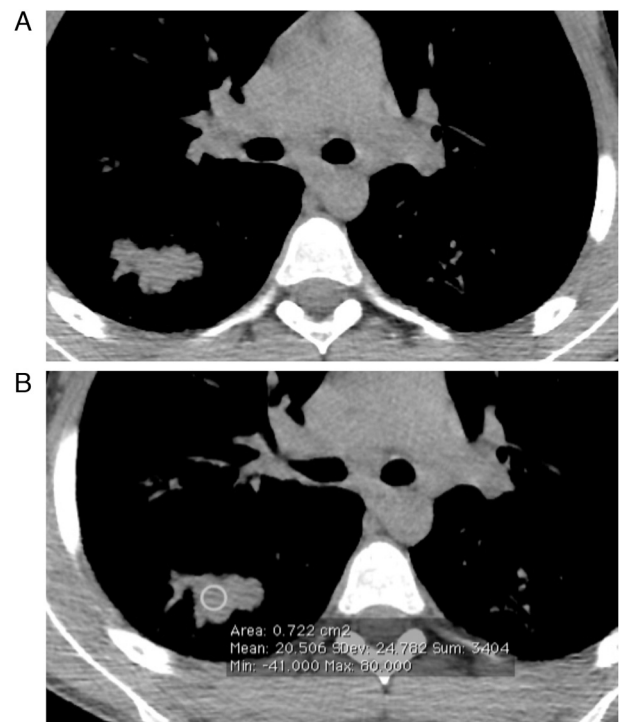


Fig. 2. Axial CT image of the chest on mediastinal window: patient 1, ABPA –. A. Right postero-basal central bronchocele, B. Low-attenuation bronchocele: ROI, mean HU = 20.506.

fibrosis, this variability is explained both by the diagnostic difficulty and the important variability of exposure to *Aspergillus Fumigatus* according to the geographic area [8,9]. ABPA may lead to acute worsening of the respiratory condition and ongoing decline in lung function. Without adequate treatment, ABPA ultimately progresses to a chronic state with lung fibrosis [5]. ABPA is a hypersensitivity pulmonary disease associated with inflammatory destruction of airways in response to *Aspergillus* allergens [15]. Thus, chronic airway colonization with *Aspergillus fumigatus* induces strong inflammatory responses with high IgE levels [16]. The factors leading to ABPA are not clearly understood, but it is believed that *Aspergillus*-specific, IgE-mediated type I hypersensitivity reactions and specific IgG-mediated type III hypersensitivity reactions play central roles in the pathogenesis of ABPA [6]. Furthermore, host factors, including individual susceptibility, may contribute to the immuno-pathogenesis of this condition. Early diagnosis and treatment of ABPA are important to prevent serious and potentially irreversible lung damage [7].

There is not a single gold standard test to diagnose ABPA, therefore the diagnosis in CF patients remains particularly difficult, given

overlapping clinical, microbiologic and immunologic features [15]. To diagnose ABPA in cystic fibrosis patients from a positive skin-prick test to *Aspergillus fumigatus* is not possible [17]. The imaging findings in patients with ABPA and CF are also similar: distribution of bronchiectasis, pulmonary infiltrates and mucus plugging are present in both diseases [18]. However, a specific finding has been reported in asthmatic ABPA patients, as the presence of high-attenuation mucus (HAM) impactions in bronchoceles [19]. To our knowledge, it has not been studied in CF.

In 1992, Goyal et al. [20] first described HAM as a specific finding in asthma-ABPA patients. High-attenuation mucus (HAM) is said to be present when the density of mucus is visibly greater than that of the *para*-spinal muscles [21]. However, this finding was infrequently reported [22]. Logan et al. [23] described the occurrence of HAM plugs in 28% of patients with ABPA in their study of 14 patients over a 4-years period. Recently, Argawal et al. have thoroughly studied this feature, confirming its usefulness in establishing a positive diagnosis of ABPA and possibly indicating the degree of severity of the disease [21]. The exact etio-pathogenesis of HAM impaction is unclear. However, several hypotheses have been proposed. Hemosiderin within inspissated mucin was one of the initial agents proposed to be responsible for the HAM impaction [19]. Zinreich et al. [24] disputed this theory based on the failure to identify increased hemosiderin levels within typical allergic fungal mucin. Currently, the most widely accepted theory for HAM impactions is the presence of desiccated mucus or calcium salts with ions of manganese and iron [25,26].

HAM is rarely seen in children, and except for one case report [13] has not been reported in the literature. The two most common causes of high attenuation bronchial content in children are acute hemorrhage and aspiration of dense foreign-object [13].

Because low-attenuation mucus pluggings are often present on CT scans of CF patients, we hypothesized that the presence of high-attenuation plugs on CT scans could be an interesting indicator of the diagnosis of ABPA. The attenuation value of the *para*-spinal muscle proposed in the literature as the cut-off indicator for “HAM” is a rather elevated threshold usually around 65 HU [21]. Furthermore it varies from subject to subject and is a subjective appreciation. We thought that an objective criterion such as the density measurement of the bronchial content may be a better and more sensitive way of classifying patients into HAM and non-HAM categories.

Our study suggests that bronchoceles density measurement can be indeed a very interesting discriminating criterion in the evaluation of CF complications. It is easily performed on CT scan and should probably be done systematically in the presence of mucoid impactions.

The results obtained in our small series are encouraging, but although all patients with bronchocele density > 36 HU were positive for ABPA, the small sample size precluded us to perform a robust ROC analysis and provide significant sensitivity and specificity results. However, this preliminary retrospective study will open the way to larger multicenter and prospective studies that could further refine the optimal threshold for diagnosing ABPA.

Considering bronchocele densities measurement, there are however some difficulties to overcome.

Although simple density measures can be performed easily and routinely, small ROI may be difficult to place properly and may not be feasible in every mucoid impaction.

We also realized that movement's artefacts could induce false-positive hyperdensity areas (Fig. 3). It is therefore mandatory to take the measurements on mediastinal windows with a close observation of lung windows at the same level to detect these artefacts. In this situation, the hyperdensity appears more focally within the bronchocele, where the lung windows appear blurred, whereas the cases we encountered in ABPA revealed diffuse hyperdensity of the entire bronchocele content.

Most CT-scans performed in follow-up evaluation of cystic fibrosis are realized without IV contrast, only two CT-scans were enhanced in our study, which did not allow statistical analysis on the subject.

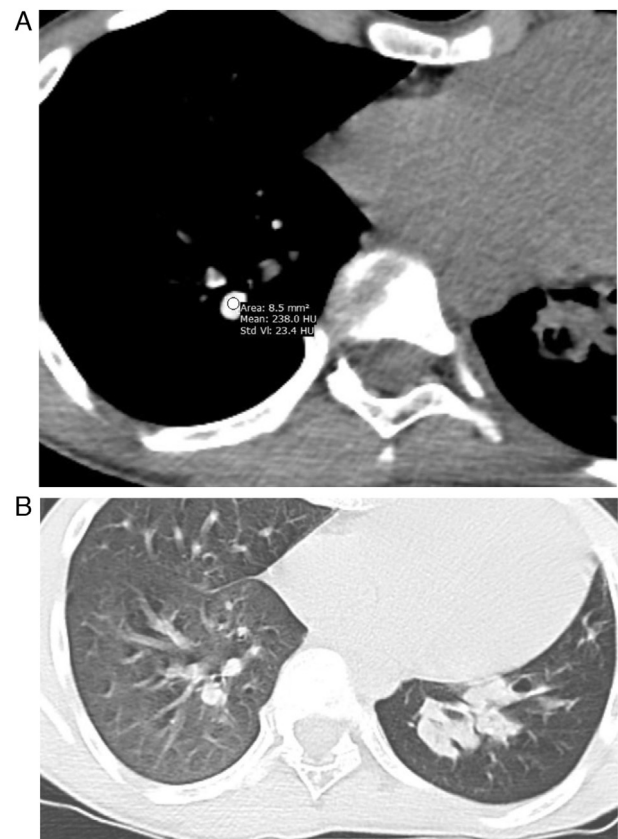


Fig. 3. Axial CT image of the chest: false positive high-attenuation mucoid impaction (ROI, mean HU = 238), secondary to important movement artefacts best seen on lung windows. This patient was suffering from bronchiectasis secondary to a previous infection; he was not part of our study but illustrates the fact that measurement on mediastinal window should always be interpreted accordingly to possible artefacts depicted only on lung window. A. Mediastinal window: false positive hyperdense bronchocele secondary to movement artefacts, B. Lung window: right postero-basal movement artefacts blurring the picture and creating an area of hyperdensity.

However it is possible that enhancement of bronchial wall might increase the density measurements of bronchocele content if the ROI is not correctly placed centrally, away from bronchial wall. The small frequency of bronchoceles discovered on enhanced CT-scans might not allow proper assessment of this possible bias, but the fact that non-enhanced CT-scan is the routine technique for this condition tempers the problem.

Therefore, examining precisely the appearance and density of bronchoceles appears very informative and magnetic-resonance imaging (MRI) being an increasing tool in the assessment of CF [27,28] it could be also interesting to evaluate the signal intensity of bronchoceles on MR imaging where HAM could appear as hypointense on T2 weighted images according to what is found in fungal sinusitis [24].

Overall, on chest CT-scan, the density measurement of bronchoceles content may become a marker of CF complicated with ABPA. In our series, density > 36 HU seemed to be associated with ABPA. Thus, systematic density measurements of bronchoceles on follow-up CT-scans of patients with CF could help to raise this difficult diagnosis and may contribute to the existing list of imaging criterion for the diagnosis of ABPA. Larger multicenter series could further refine the optimal HU threshold, and MRI assessment of bronchocele content could also enhance the diagnostic value of imaging techniques in this population of patients.

Disclosures

All authors have disclosed no financial interests, arrangements or

affiliations in the context of this activity.

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