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ORIGINAL ARTICLE

Pulmonary complications in patients with antibody deficiency

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Abstract
Objective: The aim of this study was to evaluate pulmonary complications in patients with primary antibody deficiency (X-linked agammaglobulinaemia [XLA] and common variable immunodeficiency [CVID]).
Methods: Thirty patients over six years of age regularly followed in a reference out-patient clinic on primary immunodeficiency were studied. All of them have been treated with intravenous immunoglobulin (IVIG) replacement therapy. Pulmonary complications were evaluated analysing clinical data (medical records review), lung function test (spirometry) and pulmonary imaging (chest computed tomography [CCT]).
Results: Patients with normal CCT (N=14) and those with abnormal CCT (N=16) have shown no differences regarding the age at onset of symptoms, age of diagnosis, and duration of IVIG treatment. The mean number of pneumonia episodes before IVIG replacement was significantly higher among patients with abnormal CCT (4 vs 7 episodes, p=0.008). CCT abnormalities observed in 16 patients were: bronchiectasis (12/16); peribronchial thickening (3/16); air trapping (5/16); lung volume reduction (4/16); atelectasis (2/16), follicular bronchiolitis and ground-glass abnormality (2/16) and parenchyma nodule (1/16). Lung function tests showed ventilatory disturbance in 18/30: obstructive pattern in 38.8%, restrictive pattern in 44.4%, and mix pattern in 16.7%. There were no significant differences in lung function between those with and without CCT abnormalities. Negative significant correlations were observed between lung function and number of episodes of pneumonia. Chronic persistent cough was associated with a reduction in lung function.
Conclusions: Pulmonary complications are not rare in patients with antibody deficiencies and they must be monitored.

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Introduction

Antibody deficiencies such as X-linked agammaglobulinaemia (XLA) and common variable immunodeficiency (CVID) are characterised by low levels of serum immunoglobulins and impaired antibody production.[1,2]

Recurrent respiratory bacterial infections, even with appropriate treatment, are important features of XLA and CVID, particularly those by encapsulated bacteria such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Staphylococcus sp*.[3,4] A high proportion of these patients experienced at least one episode of pneumonia before diagnosis, and many, multiple episodes.[5,6] In fact, respiratory infections are responsible for chronic symptoms, reduction in quality of life, frequent use of antibiotics, hospitalisations and anatomical lung abnormalities, representing one of the main causes of death in these patients.[4,7]

The early diagnosis of chronic pulmonary diseases in patients with XLA and CVID is essential in preventing further infections and complications. Lung function (LF) tests and imaging are the most suitable tools for this investigation.[3,8] Chest computed tomography (CCT) has shown to be more sensitive than traditional X-rays in detecting lung abnormalities, such as bronchiectasis.[9,10]

The aim of this study was to compare features of patients with primary antibody immunodeficiency on treatment with IVIG with and without pulmonary abnormalities.

Methods

Thirty patients (22 males) over six years of age and diagnosed as XLA and CVID were included in this study. Diagnosis of XLA and CVID was established according to PAGID criteria.[11] All have been followed in the Division of Allergy and Clinical Immunology, from the Federal University of São Paulo, Brazil, as out-patients in regular intravenous immunoglobulin (IVIG) replacement therapy. None of the patients were smokers. Clinical data were obtained from a questionnaire and medical records.

LF tests (spirometry, Vitalograph Spirotrac III, 1.31) were performed in the morning, according to standard recommendations, after daily device calibration of equipment.[12] Three acceptable flow-volume maneuvers were obtained from each patient before and 15 minutes after 400mcg of inhaled salbutamol (MDI). LF values were expressed in relation to standard values as percentage of predicted.[13] Bronchodilator responsiveness was considered positive if there was at least a 12% increase in forced expiratory volume in the first second (FEV_1). Abnormal lung function was defined by the presence of FEV_1, forced vital capacity (FVC) or the ratio between FEV_1 and FVC (FEV_1/FVC) values below 80% of predicted or forced expiratory flow at 25 to 75% of FVC ($FEF_{25-75\%}$) below 70% of predicted.

CCT (inspiratory- and expiratory-high resolution scans) was performed when the patients were free of acute respiratory infections for at least two weeks. Non-parametric tests were employed in the statistical analysis and p values lower than 5% were interpreted as statistically significant. The study was approved by the Ethical Committee of the institution and an assigned written informed consent was obtained from all patients or their guardians.

Table 1 Main characteristics of patients according to the presence or absence of abnormalities in chest computed tomography.

Characteristics	Chest computed tomography	
	Normal	Abnormal
N	14	16
Male/Female	12/2	10/6
Diagnose (XLA/CVID)	4 / 10	4 / 12
Age (years)[a]	19.6 (7 — 52)	22.5 (8 — 42)
Age at diagnosis (years)[a]	16.0 (1 — 42)	16.0 (1 — 34)
Delay of diagnosis (years)[a]	6.7 (0 — 15)	7.9 (0 — 25)
IVIG treatment (years)[a]	9.0 (0 — 26)	6.0 (1 — 21)
Chronic cough	0	9

[a] Mean and range; XLA — X-linked agammaglobulinaemia; CVID — Common variable immunodeficiency.

Results

Patient's clinical data are shown in Table 1. Normal CCT was observed in 14 patients and abnormal in 16 patients. 80% of patients without CCT abnormalities and 60% of those with CCT abnormalities had developed infections and needed antibiotic treatment early in infancy. The median number of pneumonia per patient before IVIG replacement was seven and four for patients with and without CCT abnormalities, respectively (p=0.008). Two patients without CCT abnormalities had not presented pneumonia before diagnosis. Age of diagnosis varied from 1 to 42 years (mean 16 years) in those without CCT abnormalities and from 1 to 34 years (mean 16 years) in those with CCT abnormalities (p>0.05). The median delay in diagnosis, from the age of the first infection treated with antibiotics to the age of the diagnosis, was 6.7 years for patients without CCT abnormalities and 7.9 years for those with CCT abnormalities (p>0.05). Delay in diagnosis was higher than 10 years for five patients, all with CCT abnormalities. Three of them referred approximately 10 episodes of pneumonia before diagnosis and they were those patients with the most severe pulmonary sequel. Chronic cough (more than six weeks) was observed in nine patients with CCT abnormalities and was absent in those with normal CCT (p=0.0009).

The most common bacterial infections during the follow-up in our Division with IVIG treatment were: sinusitis (58.0%), otitis (21.0%), infected bronchiectasis (17.0%) and pneumonias (4.0%). Persistent cough was the most prevalent respiratory symptom (9/30). Patients with chronic cough were more likely to need continuous antibiotic treatment (78% vs 29%, p=0.02) and have some LF impairment (44% vs 8%, p=0.04) than those without cough.

CCT scan was performed in all 30 patients and 53% (16) of them presented abnormalities: bronchiectasis (12/16); peribronchial thickening (3/16); air trapping (5/16); lung volume reduction (4/16); atelectasis (2/16), follicular bronchiolitis and ground-glass abnormality (2/16), and parenchymal nodule (1/16). Bronchiectasis was seen most frequently in the right middle lobe (66.7%). Seven patients were diagnosed as having more than one abnormality on CCT. The majority of patients with CCT abnormalities already presented them at diagnosis. The only patient who developed bronchiectasis

during the follow up was a XLA patient who started IVIG when he was four years old and had diagnosis of bronchiectasis at the age of 15 years old.

Two patients with diagnosis of follicular bronchiolitis and ground-glass abnormality presented severe lung dysfunction (patients # 25 and 26). One of them passed away at the age of 33 due to pulmonary complications (patient # 25). CVID was diagnosed when he was 16 years old and he already presented bronchiectasis and severe LF impairment. Despite treatment with high doses of IVIG (600-800 mg/kg/doses), and supportive drugs, his lungs progressively worsened and lung biopsy showed herpes virus (patient # 25). The other patient (# 26) also presented bronchiectasis when CVID was diagnosed 17 years ago. His condition is deteriorating with respiratory insufficiency unresponsive to treatment. Last CCT showed ground-glass opacity and follicular bronchiolitis. This patient had pulmonary tuberculosis before diagnosis of CVID.

Table 2 Lung function parameters (% of predicted) and chest computed tomography (CCT) findings in patients with antibody deficiency.

Patient	FVC	FEV_1	FEV_1/FVC	$FEF_{25-75\%}$	CCT
1	88.1	84.9	96.4	76.9	normal
2	95.1	69.5	73.0	32.4	normal
3	83.2	80.3	96.5	66.5	normal
4	105.0	86.7	82.5	57.9	normal
5	90.1	97.4	108.0	91.3	normal
6	91.4	93.3	102.0	94.4	normal
7	54.6	51.8	94.7	45.3	normal
8	99.7	95.3	95.6	66.2	normal
9	103.2	91.9	89.0	87.7	normal
10	83.3	86.4	103.6	99.6	normal
11	82.0	84.0	86.0	89.0	normal
12	99.0	80.0	82.0	90.0	normal
13	73.0	73.0	99.0	70.0	normal
14	83.0	78.0	86.0	82.0	normal
15	69.6	71.5	102.7	72.5	a
16	84.3	84.1	99.7	74.4	a
17	72.9	74.2	101.8	103.9	c
18	69.5	67.5	97.0	58.8	f
19	97.8	98.2	100.4	98.3	e
20	111.5	109.3	98.0	109.0	a,f
21	63.3	58.9	92.9	37.3	a,c
22	59.9	47.3	78.9	24.9	a,f
23	109.0	98.7	90.5	87.6	a,d
24	61.5	31.8	51.8	8.8	a,b,d
25	41.6	23.7	57.0	5.7	a,d,f
26	46.2	44.6	96.5	35.3	a,d,f
27	87.0	77.0	87.0	51.8	a
28	65.0	65.0	97.4	56.9	a
29	91.0	88.0	99.0	83.0	b
30	81.0	75.0	80.0	71.0	b

FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; FEF25-75%: forced expiratory flow at 25 to 75% of FVC; a: bronchiectasis; b: peribronchial thickening; c: atelectasis; d: lung volume reduction; e: parenchymal noduli; f: air trapping.

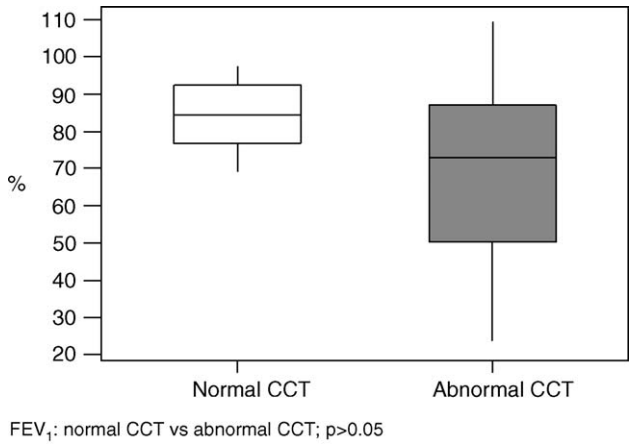

Figure 1 Boxplot of FEV_1 values of patients with normal (white box) and abnormal (grey box) chest computed tomography (CCT).

IVIG doses ranged from 333 to 550 mg/kg in those without CCT abnormalities and from 400 to 800 mg/kg in those with CCT abnormalities. Three patients with CCT alterations and ten with normal CCT were taking continuous antibiotics.

All patients performed acceptable flow-volume maneuvers. Eighteen (60.0%) had some ventilatory disturbance with an obstructive pattern in seven (38.8%), restrictive pattern in eight (44.4%), and combined in three (16.7%). Individual LF parameter values are shown in Table 2. No patient showed an increase in LF parameters after receiving an inhaled bronchodilator.

There was a negative significant correlation between FVC values and age of diagnosis ($r = -0.37$; $p=0.04$) and the number of pneumonias ($r = -0.49$; $p=0.006$). Values of FEV_1 showed negative significant correlation with the number of pneumonias ($r = -0.48$; $p=0.008$). There was no significant difference in LF values between those with or without CCT abnormalities (Fig. 1). Similar results were observed for the presence or absence of bronchiectasis (data not shown). Despite these analyses, patients classified as having persistent cough had lower FVC (median: 63% vs 88%; $p=0.003$), FEV_1 (median: 59% vs 84%; $p=0.003$, Fig. 2), and $FEF_{25-75\%}$

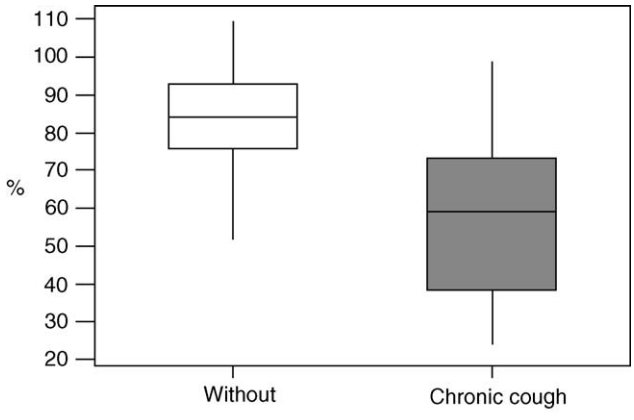

Figure 2 Boxplot of FEV_1 values of patients with (grey box) and without (white box) chronic cough.

(median: 37% vs 82%; p=0.004) when compared to those without persistent cough. These patients also presented a significant higher number of pneumonias (median: 4 vs 10; p=0.01). Among the 12 patients with bronchiectasis five of them had normal LF parameters and seven referred chronic cough.

Discussion

The respiratory system is the main target of infections in patients with antibody deficiencies. Pneumonia was the most common infection before IVIG replacement therapy and sinusitis has been the most frequent during it.[6,14] Although the replacement of IVIG can significantly decrease the frequency and severity of infections in patients with CVID,[7] progression of pulmonary sequel still occurs despite adequate treatment.[2,15] Both XLA and CVID patients were enrolled in this study and were distributed in both groups. Compared with XLA, patients with CVID appear to have a greater likelihood of developing lung disease, possibly because patients with XLA are diagnosed and treated earlier than those with CVID, in those the diagnosis is frequently delayed.[5]

Patients were grouped according to the presence or absence of CCT abnormalities in order to identify some events that could explain pulmonary sequel. Clinical features, mean age of diagnosis, and IVIG treatment were similar in both groups. One interesting point is that all patients but one from the group with CCT abnormalities already had such finding at the time of diagnosis reflecting the importance of an early diagnosis.

We observed that the number of pneumonias before diagnosis was the most sensitive parameter for CCT alterations. Although the delay in diagnosis did not differ between the two groups, fact also reported by others,[6,16] it is the most probably explanation for the higher number of pneumonias presented by patients with abnormal CCT.[4] The delay in diagnosis is justified in part by the low prevalence of these diseases, and consequently by the low index of suspicion. Moreover, the different type and pictures of these infections, commonly treated by different specialists, could mask and underestimate these patients' increased infection liability.[17] Some patients look for treatment only for acute infections and are assisted by different physicians in the emergency room which decreases the suspicious of primary immunodeficiency diseases.

CCT has been pointed out as one of the best tools to evaluate pulmonary complications in patients with antibody deficiency, mainly because it is non-invasive and has a high sensitivity in detecting pulmonary anatomic lesions.[8]

A high percentage of patients with CCT abnormalities had chronic cough despite adequate IVIG therapy replacement and antibiotics. It is presumed that persistence of respiratory symptoms could be due to irreversible pulmonary lesions which occurred before treatment or due to a bronchial inflammatory process non-responsive to the standard treatment[15] or even by virus infections.[2] The chronic persistence of microorganisms in lower airways may be a contributory factor in the development of bronchial damage in CVID patients. Herpes virus was isolated in lung biopsy from one of our patients who passed away. Human Herpes virus 8 has been associated with granulomatous-lymphocytic interstitial lung disease (GLILD) which is a combination of granulomatous and lymphoproliferative (LIP, follicular bronchiolitis, and lymphoid hyperplasia) lung disease. Patients with GLILD exhibited a restrictive ventilatory pattern and a decreased median survival rate, compared to those without it.[18]

Few studies have evaluated the relationship between the presence of lung lesions and chronic symptoms in patients with antibody deficiency, and the majority of them have failed in showing such relationship.[2] Rusconi et al. evaluated 24 patients with primary hypogammaglobulinaemia and chronic cough (for over 3 months) and verified that 67% of them had lesions on a CCT scan. The CCT alterations were scored (Bhalla's severity score) and compared with respiratory symptoms. They observed a significant correlation only in those patients with more severe disease.[15]

The evaluation of LF by spirometry is considered simple and highly feasible in patients with antibody deficiency older than six years of age. All of our patients have performed reproducible LF tests, and a characteristic spirometric pattern was not observed. There were patients with obstructive dysfunction, others with restrictive, and some with a combined pattern similar to the observed by others.[8] Some patients reported improvement of pulmonary symptoms after regular use of long acting beta2 agonists but none of them showed significant increase in LF values after bronchodilator.

We expected that patients with anatomical pulmonary lesions would present the lowest values of LF, but this was not the case (Fig. 1). The few number of patients evaluated does not authorise us to take definitive conclusions about this relationship which remains a controversial issue in the literature.[2,9,19,20]

The high prevalence of LF abnormalities and of CCT lesions in these patients, as well as the absence of association between these findings, highly suggests that lung function testing and imaging are useful, necessary, and complementary in the evaluation of pulmonary complications in patients with antibody deficiency.

Conflict of interest

The authors have no conflict of interest to declare.

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