High resolution computed tomography and pulmonary function in common variable immunodeficiency

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Summary
Patients with common variable immunodeficiency (CVID) have impaired production of immunoglobulins and hence recurrent airway infections, which in turn may lead to radiological changes and impaired lung function. Uncertainty exists about the nature and frequency of the radiological and the physiological abnormalities, and how they relate to each other. We reassessed high resolution computed tomography (HRCT) images in 65 patients, reported results from previously measured lung function tests, and studied relations between radiology, function and clinical variables. Airway obstruction, ventilatory restriction and impaired gas diffusion was found in 40, 34 and 21% of the patients, respectively. HRCT abnormalities were present in 94% of the subjects, mild changes being the most common. Bronchial wall thickening, found in two thirds of the patients, was related to airway obstruction and impaired gas diffusion. Linear and/or irregular opacities, the most frequent interstitial abnormality, was related to impaired gas diffusion. Bronchiectasis was found in more than half, but only severe bronchiectasis was related to airway obstruction. Since bronchial wall thickening and linear and/or irregular opacities are both frequent and important determinants of impaired pulmonary function, more attention should be given to these features in the follow up of CVID patients.
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Introduction

Common variable immunodeficiency (CVID) is a primary immunodeficiency disease characterised by impaired production of immunoglobulins and recurrent airway

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infections, which in turn may lead to chronic pulmonary damage. T cell and macrophage/monocyte abnormalities are also common and likely contribute to the increased incidence of autoimmune diseases seen in these patients.[1]

Bronchiectasis, a frequent finding on high resolution CT (HRCT) in CVID, is usually accompanied by airflow limitation and is probably the cause of daily cough and sputum.[2,3] Non-infectious pulmonary manifestations such as granulomatous and lymphoproliferative disorders (e.g. lymphocytic interstitial pneumonia and organising pneumonias), often visualised as HRCT abnormalities of the lung interstitium, may lead to reduced lung volumes and gas diffusion.[4,5] The pathogenesis of the pulmonary damage in CVID is not clear, but probably complex.

Reports from previous studies of HRCT in CVID reveal that there is no complete agreement on which abnormalities to be assessed.[5-7] As a consequence, uncertainty exists about the nature and occurrence of CT abnormalities in CVID, and how these relate to pulmonary function. The majority of the diagnosed CVID patients in Norway has a regularly follow up at our clinic, Rikshospitalet University Hospital, which is a reference hospital for adult patients with primary immunodeficiency syndromes in Norway.[8] The follow up includes pulmonary function tests and HRCT annually or every 2nd year. IgG replacement therapy in our patients includes subcutaneous (SCIG) or intravenous (IVIG), or both.[9,10]

The objectives of the present study were to examine the nature and frequency of radiological abnormalities and their relations to pulmonary function in a relatively large group of patients with CVID.

Patients and methods

Patient selection

In this retrospective, cross sectional study, 92 patients with CVID who were or had been followed at our hospital up to 2004, were initially included. These constituted approximately 80% of the Norwegian CVID patients.[8]

The diagnosis of CVID was in accordance with WHO diagnostic criteria[11] with serum levels of at least two of the three Ig isotypes (IgG, IgA, IgM) two standard deviations or more below mean of the age, onset of immunodeficiency at greater than 2 years of age, and other causes of hypogammaglobulinemia having been excluded. The float diagram in Fig. 1 shows the procedure for selection of the final study group of 65. These patients (29 women and 36 men), had performed both pulmonary function tests (PFT) and HRCT within a short time span (median 0, range 0–13 months). Patients who had used antibiotics were included if they had stopped at least 1 week before PFT or HRCT examination. Information about demographic and clinical data was extracted from the patient records.

Pulmonary function tests (PFT)

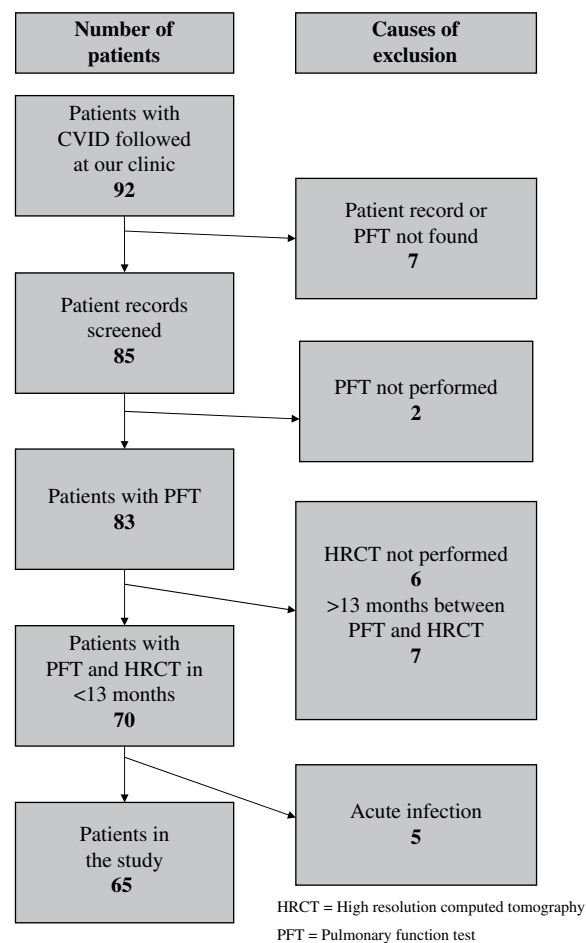PFT's had been performed on a Vmax Pulmonary Function Unit (ViaSys, Santa Ana, CA, USA) in accordance with

Figure 1 Float diagram showing procedure for selection of the final study group.

ERS guidelines.[12] Pulmonary function variables included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and FEV_1/FVC. Diffusing capacity (DLCO), adjusted for haemoglobin, and alveolar volume (VA), had been measured with the single breath carbon monoxide test. VA was taken as a substitute for total lung capacity (TLC). The predicted values were those of ERS 1993 update.[12]

High resolution computed tomography

The HRCT examinations had been carried out as routine investigations, with a HiSpeed CT/i scanner (GE Medical Systems, Milwaukee, WI, USA). The images were obtained at 120 kV and 200–240 mA with 1 mm collimation at 10 mm interval and reconstructed with a high-spatial-frequency (bone) algorithm. If inspiratory scans showed signs of airway disease, expiratory scans were performed. This was the case in 54 patients. Readings were performed in consensus on a picture archiving and communication system (PACS) screen by two experienced chest radiologists (TMA and GM) without prior knowledge of patient history or lung function. In cases where the two radiologists disagreed, a third was consulted. One half of the images were assessed

twice, for calculation of inter-observer agreement. A modified Bhalla score[13] was applied to determine the type, presence and severity of 12 radiological abnormalities, six airway and six interstitial abnormalities (see Appendix 1). The severity and/or extent of these was assigned a score of 0– 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe). For nodules and micro-nodules a scoring system for interstitial changes in occupational disease was used,[14] and recoded into four groups of Bhalla (0–3). If an abnormality was present, the most frequent score (1, 2 or 3) was selected.

For bronchiectasis, the severity was expressed as the broncho-arterial ratio, which is the diameter of the bronchial lumen divided by the diameter of the adjacent pulmonary artery. Bronchiectasis was defined as present if the ratio was equal to or greater than 1.[15] Loss of tapering is one of the diagnostic criteria of bronchiectasis on spiral scans. Since HRCT does not include the whole lung volume, loss of tapering was not used as a specific criterion in this scoring system. Bronchial wall thickening was expressed as the sum of thickness of the bronchial wall on both sides of the lumen divided by the diameter of the adjacent artery. If the ratio was 0.5 or greater, the bronchial wall was defined as thickened.[16] The presence of mucus plugging and centrilobular nodules, air trapping, nodules and micro-nodules, linear and/or irregular opacities, consolidations, ground glass opacities, honeycombing and emphysema was based on established criteria.[17,18] The sum of scores for 10 HRCT abnormalities (air trapping excluded) was calculated (maximum possible score = 30).

Statistical methods

The statistical software package (SPSS version 14.0.2) was used for the analysis. Statistical significance was set at level of $p < 0.05$. Relationship between two continuous variables was tested by Pearson's or Spearman's correlations. Analysis of variance with Tukey as a post hoc test was used to explore the relationship between HRCT scores (0–3) and pulmonary function. CT scores were recoded to two groups only, those with and without a given abnormality (0/1). Two sample T-tests or Mann–Whitney were used to compare means or medians of continuous data, Chi square and Fisher's test for groups with categorical data. Multiple linear regression was used to explore the relationship between recoded HRCT scores (0/1), clinical and demographic variables and pulmonary function in combination with the variable selection strategies for forward and backward selection. The criterion for introduction and removal of variables was $p < 0.05$. Assumptions concerning regressions were satisfactory. Cohen's Kappa scores for inter-observer agreement were calculated.[19]

Ethics

The study was conducted according to the ethical guidelines at our hospital, which comply with the Helsinki declaration, and was approved by the hospital's authorised representative.

Results

Patients and demographics

All patients were Caucasians. Median (range) age was 48 (20–78) years. Table 1 shows the frequency of some extrapulmonary manifestations, smoking habit, infections, productive cough and anti-asthmatic medication. At the time of PFT, median serum level of C-reactive protein (CRP) was 6 mg/l (range 1–108.0 mg/l), slightly higher than the reference value (<4 mg/l). The leukocyte count varied from 1.0 to 14.0×10^9/l with 21–86% neutrophils and 7–54% lymphocytes. The dosage immunoglobulins ranged from 0.1 to 2.0 g/kg/4 weeks. Serum IgG level was 8.3 (2.9) g/l, which is within the normal range (5–15 g/l).

HRCT

Only 6% of the patients had completely normal HRCT images. Table 2 shows that bronchial wall thickening, bronchiectasis and air trapping were the most frequent airway abnormalities, found in 68, 57 and 54% of the patients, respectively. Twenty-six patients (40%) had both bronchiectasis and bronchial wall thickening. In the parenchyma, linear and /or irregular opacities and nodules and micro-nodules were the dominant findings, seen in more than 50% of the patients. The majority (40%) of the nodules were small (diameter less than <1.5 mm). In contrast to these findings, ground glass opacities and emphysema were seen in only 12% of the patients. The mean Kappa scores for the dichotomous HRCT abnormalities (score 0 vs. $1 + 2 + 3$) was 0.51, ranging from 0.28 with mucus plugging and centrilobular nodules to 0.89 for emphysema. The Kappa scores for bronchiectasis, bronchial wall thickening and linear and/or irregular opacities were 0.56, 0.50 and 0.42 respectively. Except for the

Table 1	Clinical characteristics in 65 patients with CVID.	
Variable	Number of patients	%
Splenomegaly[a]	30	46
Granulomatous disease[b]	7	11
Haematological abnormalities[c]	24	37
Other autoimmune disease[d]	28	43
Gastrointestinal symptoms[e]	28	43
Productive cough		
Males	20	30
Females	8	12
>2 bacterial infections last year	21	32
Daily or current smoking	27	41
Inhaled steroids	14	22
Beta2agonist	20	30

[a] Length >13 cm on ultrasound or CT examination. Includes spleenectomised.
[b] Non-caseating granulomata in various tissue biopsies.
[c] E.g. neutropenia, anemia, thrombocytopenia.
[d] E.g. arthritis, thyroiditis.
[e] E.g. mal absorption, diarrhoea.

Table 2 Distribution of scores on HRCT abnormalities in 65 patients.

		HRCT abnormality				
		Score 0 n	Score 1 n	Score 2 n	Score 3 n	With abnormality %
Airways						
1	Bronchiectasis; severity	28	23	7	7	57
2	Bronchial wall thickening	21	33	8	3	68
3	Bronchiectasis; extension	28	22	8	7	57
4	Bronchiectasis: axial distribution	28	1	26	10	57
5	Mucus plugging and centrilobular nodules	49	11	3	2	25
6	Air trapping n = 54	26	21	3	5	54
Interstitium						
7	Nodules and micro-nodules	32	21	10	2	51
8	Linear and/or irregular opacities	30	25	3	7	53
9	Consolidation	41	20	3	1	37
10	Ground glass opacities	53	6	3	3	12
11	Honeycombing	49	3	2	1	9
12	Emphysema	53	6	2	4	12

See Appendix 1 for score-system.

abnormalities mucus plugging and centrilobular nodules and ground glass opacities, the 95% confidence intervals did not include zero.

Pulmonary function

Table 3 (column 1) shows that the upper limit of the confidence intervals for FEV_1, VA, DLCO and DLCO/VA were below 100%, indicating both airway obstruction, restriction and diffusion impairment in the group as a whole. The distribution of FEV_1 and FEV_1/FVC were slightly skewed. In 40% of the patients, the FEV_1/FVC ratio was lower than 0.7, usually regarded as the lower limit of normal. VA and DLCO/VA were lower than 80% of predicted in 30 and 21% of the patients, respectively. Taken together, the patient group was characterised by airway obstruction in 40%, impaired gas diffusion in 21% and ventilatory restriction in 34%.

Relation between pulmonary function, HRCT findings and clinical variables

Univariate analysis of variance (ANOVA) showed that FEV_1 and/or FEV_1/FVC differed significantly between the scores (0–3) of severity and extension of bronchiectasis, bronchial wall thickening, air trapping and mucus plugging ($p = < 0.05$).

Multiple bivariate analyses after recoding of the CT scores to binary variables (present/ not present) showed that the occurrence of mucus plugging, air trapping and bronchial wall thickening were related to decreased FEV_1/FVC, FEV_1 and/or FVC. Bronchial wall thickening was also significantly associated with a decrease in DLCO and DLCO/VA, as were the linear and /or irregular opacities, ground glass opacities, honeycombing and emphysema. As an example, column 2 and 3, Table 3, show the differences in pulmonary function between those with and without bronchial wall thickening and linear and/or irregular opacities, the two most frequent HRCT abnormalities. There was no association between the occurrence of bronchiectasis and any of the pulmonary function variables.

No relationship was found between pulmonary function and CT findings on one hand, and age, sIgG, CRP, leukocyte count, smoking habit, productive cough or extrapulmonary manifestations on the other. In contrast, the occurrence of more than two respiratory tract infections during the last year before the PFT, was associated with a decrease in DLCO and DLCO/VA. Males had lower FEV_1/FVC than females, while females had lower DLCO.

Corrections for multiple analyses were not performed since the analysis was extended to multiple linear regression

Table 3 Pulmonary function in 65 patients, and comparison between those with and without bronchial wall thickening and linear and/or irregular opacities.

Pulmonary function		Total		Bronchial wall thickening			Linear and/or irregular opacities		
		L (SD)	% pred (95% CI)	Yes % pred	No % pred	p	Yes % pred	No % pred	p
FVC	Mean	4.0 (1.2)	99.4 (94.5,104.3)	96.1	106.1	0.019	99.6	99.1	0.910
FEV$_1$	Mean	2.8 (1.0)	85.5 (79.8, 91.7)	80.0	97.9	0.001	85.6	86.0	0.952
FEV$_1$/FVC	Mean	70.9[a] (13.5)		68.6	75.8	0.043	70.3	71.2	0.852
DLCO	Mean	7.8[b] (2.9)	78.9 (84.2, 92.5)	73.8	90.4	0.005	73.6	85.0	0.039
VA	Mean	5.6 (1.6)	88.4 (84.2, 92.5)	86.0	93.6	0.093	88.9	87.8	0.792
DLCO/VA	Mean	1.4[c] (0.4)	89.9 (84.6, 95.1)	86.3	97.8	0.043	82.6	98.1	0.003

L: Liter. %: pred = percent of predicted (ERS 1993 update).
[a] %.
[b] mmol/min/kPa.
[c] mmol/min/kPa/L.

(Table 4). HRCT abnormalities with significant relation to the pulmonary function on bivariate analysis presented in the previous paragraphs were introduced to the regressions (see text above and legend, Table 4). As an example of the results presented in Table 4, the Beta coefficient (B) in line 1 shows that FEV$_1$% predicted was 17.9 percent points lower in patient with bronchial wall thickening compared to those without ($p = 0.004$). R square adjusted shows that the presence of bronchial wall thickening could explain 11% of the variation in FEV$_1$% predicted. In summary, Table 4 shows that the presence of bronchial wall thickening was a significant determinant of lower FEV$_1$ and DLCO, emphysema was a determinant for lower FEV$_1$/FVC and DLCO/VA, mucus plugging related to lower FEV$_1$/FVC, honeycombing to lower DLCO and the presence of linear and or irregular opacities was a determinant of lower DLCO/VA. Finally females had lower DLCO than males and the presence of more than two annual infections was related to lower DLCO/VA. The differences in time between CT scans and pulmonary function tests have been controlled for.

Excluded patients

Median sum of HRCT scores for the five patient excluded due to infection was 9 (range 0—18) which was significantly higher than 5 (range 0—18) for the patients in the study ($p = 0.018$). FVC, FEV$_1$ and VA % predicted were lower in these five excluded compared to the included ($p = 0.000$, 0.035 and 0.003). For the 13 patients excluded due to lack of HRCT within 13 months from PFT, the means of the pulmonary function variables were not significantly different from the 65 patients studied ($p = 0.377—0.900$).

Table 4 Determinants of pulmonary function analysed by linear regression in 65 patients with CVID.[a] [b]

Dependent variable	Unit	Variable in the equation	B	95% CI	p	R square adjusted
FEV$_1$	% pred	Bronchial wall thickening	−17.9	−30.1, −5.8	0.004	0.11
FEV$_1$/FVC	% pred	Mucus plugging	−14.2	−20.7, −7.7	0.000	0.30
		Emphysema	−13.3	−20.5, −6.1	0.000	
DLCO[c]	% pred	Bronchial wall thickening	−15.3	−25.7, −4.9	0.005	0.27
		Honeycombing	−24.2	−40.7, −7.7	0.005	
		Gender (females)	−13.6	−3.9, −23.3	0.007	
DLCO/VA[c]	% pred	Linear and/or irreg. opacities	−17.1	−26.2, −8.1	0.012	0.27
		Emphysema	−14.3	−26.3, −2.9	0.015	
		>2 infections last year	−12.2	−21.6, −2.8	0.000	

% pred = percent of predicted (ERS 1993 update). B = beta coefficient.
[a] Forward and backward regressions gave equal results.
[b] No regressions performed for FVC and VA, since bivariate analysis gave no or only on significant association. Variables (binary) which were introduced to; FEV$_1$: Bronchial wall thickening, mucus plugging and centrilobular nodules. FEV$_1$/FVC: Bronchial wall thickening, mucus plugging and centrilobular nodules, emphysema, gender. DLCO: Bronchial wall thickening, ground glass opacities, linear and/or irregular opacities, honeycombing, emphysema, gender, ><2 infections. DLCO/VA: Bronchial wall thickening, linear and/or irregular opacities, emphysema, honeycombing, ><2 infections.
[c] $n = 63$.

Discussion

In the present study we have shown that airway obstruction, impaired gas diffusion and ventilatory restriction were frequent findings in CVID patients. While multivariate analysis showed no association between bronchiectasis and impaired pulmonary function, bronchial wall thickening, seen in two thirds of the patients on HRCT, was a significant determinant of both FEV_1 and DLCO. Moreover, linear and/or irregular opacities, the most frequent interstitial abnormality, was a significant determinant of DLCO/VA.

Our estimates of reduced lung function do not differ from previous reports, since they are higher than in some studies and lower than in others.[3,20,21]

Bhalla has developed a quantitative scoring system for HRCT abnormalities related to bronchiectasis in cystic fibrosis (CF).[13] Other similar quantitative systems are now common in evaluation of both CF and non-CF related bronchiectatic diseases.[16,22–25] Using a modified Bhalla system, supplemented with scores for interstitial changes, we found that HRCT abnormalities were frequent, seen in more than 90% of the patients. This is in agreement with a study reported by Kainulainen (96%).[20] The border between normality and abnormality on HRCT is sometimes unclear, since there are few studies of normality. In addition, radiological assessment involves an element of subjectivity. In previous reports similar quantitative scoring systems for bronchiectasis have been found reliable and reproducible.[22] The Kappa scores for the most important findings in our study are generally considered as ''moderately good'',[19] indicating that our scoring system is fairly reliable.

We defined bronchiectasis as present if the broncho-arterial ratio was equal to or greater than one, while most previous studies have set the limit at a ratio greater than one.[6,23] Our choice was based on a study of healthy people in which mean broncho-arterial ratio was 0.7 (range 0.52–0.94).[26] The fact that most changes were mild, supports our choice of a more sensitive scoring system than the original Bhalla method.[13] Bronchiectasis was a frequent finding, but not as frequent as reported by Thickett (70%).[3] It is noteworthy that more than 40% of the patients did not have bronchiectasis. Furthermore, although the few patients with severe bronchiectasis (score 3) had lower FEV_1 than those with other scores, the presence or absence of bronchiectasis was not related to pulmonary function. On the other hand, even if they are a poor marker of impaired pulmonary function at an early phase, the importance of bronchiectasis should not be underestimated, since their contribution to recurrent and persistent respiratory infection and inflammation has been well established.[2,27]

We found, like Gharagozlou,[23] that bronchial wall thickening was more frequent than bronchiectasis, while others have found the opposite.[28] Thickening of the bronchial wall as a determinant of airflow obstruction has previously been reported in studies on bronchiectasis in non-CVID patients,[29] but has been given little attention in the follow up of CVID.[3,30] The fact that patients with even mild bronchial wall thickening (score 1) had lower FEV_1 than those with normal wall thickness, underlines the importance of this abnormality. Bronchial wall thickening
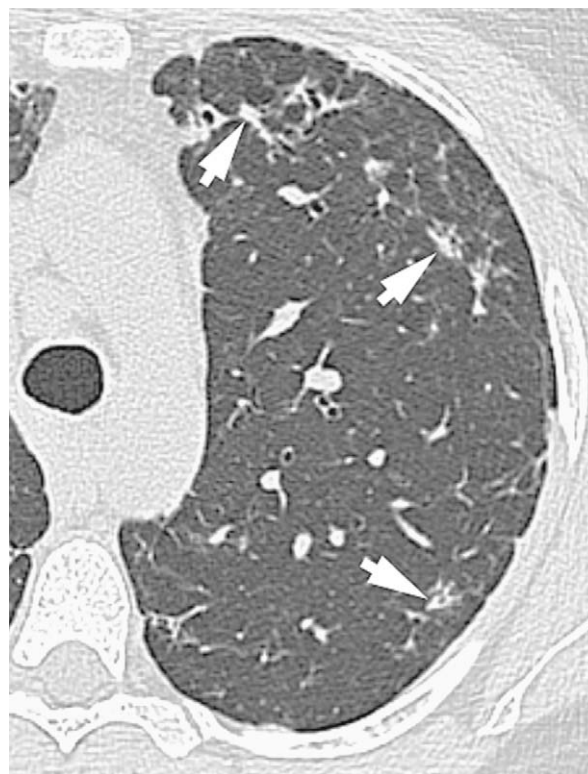
Figure 2 HRCT of left lung with linear and/or irregular opacities.

can probably be regarded as inflammatory changes extending from the large airways to the periphery, including the alveoli. This could explain the relationship to the low DLCO. Whatever the mechanism, data from the present study suggest that bronchial wall thickening should be further investigated as an early and reliable marker of impaired pulmonary function in CVID, not only as a determinant of reduced FEV_1 but also of reduced gas exchange.

Radiologically, inflammation of the large and small airways are often visualised as mucus plugging and centrilobular nodules respectively, which might explain why this abnormality was related to low FEV_1/FVC ratio. Air trapping, usually regarded as a manifestation of small airway disease, was related to impaired airway function in the univariate analysis. When it was included in the multiple regressions, it came out as a significant determinant of obstruction. However, it was not included in the final regression due to selection and insufficient patient number.

The term ''linear and/or irregular opacities'' has not been used in previous studies of CVID. This abnormality, seen in more than one half of our patients, appears as a messy picture of any linear opacity of irregular thickness which does not respect the lung architecture (Fig. 2). In previous reports of CVID this feature may has been classified as interseptal lines, consolidations, fibrosis or scars. Linear and/or irregular opacities is a well known radiological feature of interstitial pneumonias.[17] The fact that this was the most frequent interstitial finding, justifies our

choice of including it in the assessment of interstitial abnormalities. Since it was also a determinant of impaired gas diffusion, we consider this abnormality to be a key feature of pulmonary disease in CVID.

The patho-physiological mechanisms leading to abnormalities of airways and lung parenchyma in CVID are not clear. Factors involved in antibacterial defence, chronic inflammation and autoimmunity as well as genetic factors probably play a role. For instance, one study has shown that low levels of mannose binding lectin, a factor of the innate immunity, were related to increased frequency of lower respiratory tract infections and bronchiectasis in CVID.[31] Previously, we have reported an inverse relationship between a marker of inflammation, namely circulatory tumour necrosis alpha, and gas diffusion in a small number of patients ($n = 36$) with CVID.[32]

High resolution computed tomography has become a sensitive, easily accessible and fairly standardised method for detecting abnormalities in lung parenchyma and airways. On one hand, HRCT probably reflects the visible individual responses to the various pathogenic factors in CVID. On the other, HRCT in this study was a visual determinant of lung function in CVID patients adequately treated with immunoglobulins. Consequently, HRCT, together with pulmonary function tests, should remain an important tool in the clinical monitoring of these patients.

In conclusion, in a cross sectional study of 65 adult CVID patients, we found both airway obstruction, ventilatory restriction and impaired gas diffusion. Bronchial wall thickening and linear and/or irregular opacities, probably reflecting inflammatory changes, were the most frequent findings on HRCT and were significantly related to impaired lung function. To determine the impact these abnormalities might have on the further development of the disease, they should be included in further studies as well as in the clinical follow up of patients with CVID.

Conflict of interest statement

Appendix 1. Scoring system for HRCT images

	HRCT abnormality	Score 0	Score 1	Score 2	Score 3
Airways					
1	Bronchiectasis: severity	Absent	> = 1–<1.5 times diameter of adjacent artery	1.5–2 times diameter of adjacent artery	>2 times diameter of adjacent artery
2	Bronchial wall thickening	Absent	0.5–<1 times diameter of adjacent artery	1–1.5 times diameter of adjacent artery	>1.5 times diameter of adjacent artery
3	Bronchiectasis: extension	Absent	1–5 segments	6–9 segments	>9 segments
4	Bronchiectasis: axial distribution	Absent	Central	Peripheral	Mixed
5	Mucus plugging and centrilobular nodules	Absent	1–5 segments	6–9 segments	>9 segments
6	Air trapping	Absent	1–5 segments	6–9 segments	>9 segments
Interstitium					
7	Nodules and micro-nodules[a]	Absent	Mild (1–6 points)	Moderate (7–12 points)	Severe (13–18 points)
8	Linear and/or irregular opacities	Absent	1–3 segments	4–6 segments	>6 segments
9	Consolidation	Absent	1–3 segments	4–6 segments	>6 segments
10	Ground glass opacities	Absent	1–5 segments	6–9 segments	>9 segments
11	Honeycombing	Absent	1–5 segments	6–9 segments	>9 segments
12	Emphysema	Absent	1–5 segments	6–9 segments	>9 segments

[a] Each of the six lobes was given an initial score (point) from 0 to 3. The points (0–18) was then recoded into four groups (scores 0–3).

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