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Original Research

IMAGING

Lung MRI as a Possible Alternative to CT Scan for Patients With Primary Immune Deficiencies and Increased Radiosensitivity

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Background: **Patients with common variable immunodeficiency (CVID) suffer from respiratory infections leading over time to permanent lung damage. Increased radiosensitivity has been described, and clinicians should consider a risk-benefit assessment when ordering a CT scan, in that the exact level of "safe" radiation exposure is unknown.**

Methods: **Twenty-one patients with CVID were evaluated with chest CT scan, MRI, and pulmonary function tests on the same day. MRI protocol included a T2-weighted rotating blade-like k-space covering sequence (time repetition, 2,000; echo train = 27; field of view, 400 mm; flip angle, 150; slice thickness, 5 mm) on axial and coronal planes. The bronchial and parenchymal abnormalities were compared with those identified by CT scan applying a modified Bhalla scoring system to assess bronchiectasis, bronchial wall thickening, number of bronchial generations involved, mucous plugging, consolidations, emphysema, bullae, and nodules.**

Results: **CT scan and MRI findings were comparable for moderate to severe degrees of bronchial and parenchymal alterations. A low concordance was found between MRI and CT scan for lower scores of bronchial abnormalities. CT scan allowed a better identification of peripheral airways abnormalities.**

Conclusions: **Lung alterations in patients with higher radiation sensitivity, such as patients with CVID, might be evaluated by MRI, a radiation-free technique alternative to CT scan.**

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Abbreviations: BLADE = rotating blade-like k-space covering; CVID = common variable immunodeficiency

Common variable immunodeficiency (CVID) is the most frequent symptomatic antibody deficiency, characterized by low levels of serum immunoglobulins and impaired antibody response. Respiratory tract infections are the most prominent clinical problem observed at diagnosis and during follow-up. Despite IgG replacement, patients with CVID still suffer from respiratory infections leading, over time, to permanent lung damage in a high percentage of patients.[1] The most common lung alterations reported in patients with CVID are represented by bronchiectasis, bronchial wall thickening, nodules, and parenchymal opacities.[2] Moreover, CVID-associated manifestations can include granulomatous disease and lymphoproliferative disorders.[3] For these reasons, the management of patients with CVID often entails frequent radiologic examinations, such as chest CT scans.

Although radiation exposure might not be a contraindication in other patient populations with the application of low-dose chest CT scan protocols,[4,5] patients with CVID may have a fragile somatic profile, determining higher radiation sensitivity.[6-8] As the exact

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Table 1—*Clinical and Immunologic Data and Pulmonary Function Tests of 21 Patients With CVID*

Patient	Age, y	Sex	Onset Age, y	Trough IgG, mg/dL	IgA, mg/dL	IgM, mg/dL	FEV_1 (%)	FVC (%)	FEV_1/FVC	MEF_{25} (%)
1	30	M	2	694.5	35	23	3.43 (81)	4.76 (96)	0.72	4.07 (49)
2	31	M	2	833.5	0	0	1.93 (48.0)	2.87 (60.1)	0.67	2.37 (11.7)
3	43	M	19	680.0	0	0	1.61 (45.1)	2.48 (57.2)	0.64	1.98 (18.7)
4	20	F	8	583.0	0	0	2.45 (83.2)	2.71 (80.4)	0.9	2.22 (80.7)
5	58	M	25	758.0	32	32	2.23 (78.6)	3.29 (92.9)	0.67	1.41 (41.8)
6	60	F	13	835.0	6	4	1.00 (54.2)	1.25 (56.5)	0.8	1.21 (36.3)
7	15	M	2	678.33	0	0	4.61 (120.8)	5.25 (117.6)	0.87	2.56 (114.6)
8	62	M	33	671.0	0	4	1.61 (50.5)	2.69 (66.6)	0.59	1.59 (26.6)
9	41	M	22	544.0	6	4	3.58 (81.5)	5.27 (97.7)	0.67	2.5 (31)
10	49	M	8	615.5	6	5	3.71(98.3)	5.27 (113)	0.7	2.06 (55.3)
11	32	M	13	569.5	7	4	2.76 (70.9)	4.16 (90.1)	0.66	2.27 (35.5)
12	69	F	50	943.0	0	14	1.21 (54.2)	1.82 (68)	0.66	1.13 (22.8)
13	32	M	3	803.0	0	0	3.28 (83.5)	5.41 (116.5)	0.6	2.29 (25.1)
14	46	M	36	713.0	6	6	2.32 (75.2)	2.63 (70.9)	0.88	1.67 (76.9)
15	39	M	24	309	19	25	2.69 (65.6)	4.53 (91)	0.59	0.37 (15.6)
16	39	F	24	1,000	0	17	1.44 (50)	1.77 (53)	0.81	1.19 (32)
17	46	M	36	824	0	0	3.87 (118.8)	4.44 (112.8)	0.87	2.47 (139.6)
18	32	M	30	479	0	17	5.05 (109.8)	6.03 (108.9)	0.83	2.87 (106)
19	42	M	37	653	0	7	4.97 (122.0.3)	6.2 (124.9)	0.80	2.59 (112.8)
20	44	M	20	572	0	0	2.02 (54.7)	2.86 (63.9)	0.70	0.76 (36.7)
21	38	M	35	588	9	68	4.08 (99.7)	5.02 (101.4)	0.81	1.91 (81.3)

The CVID diagnosis was based on the European Society for Immunodeficiencies/Pan-American Group for Immunodeficiency definition.[15] Trough IgG is IgG level prior to the next replacement dose. CVID = common variable immunodeficiency; F = female; M = male; MEF_{25} = mid expiratory flow 25%.

level of "safe" radiation exposure is unknown, clinicians should consider a risk-benefit assessment when ordering CT scans. The validation of a safe, noninvasive, radiation-free technique is needed.

MRI of the lung has been considered experimental for many years, because of the weak signal intensity derived from lung parenchyma, leading to poor image quality. With the development of faster MRI techniques (parallel image acquisition methods), higher-gradient field strengths, matrix coils, and dedicated free respiratory sequences, high-quality examinations have become available in clinical practice[9]; therefore, the use of lung MRI has been demonstrated to be a reliable imaging method in patients with COPD, cystic fibrosis, and other lung diseases.[10-13] We have developed a dedicated MRI protocol to compare the accuracy of morphologic MRI and chest CT scan in the evaluation of lung alterations in a cohort of 21 patients with CVID.

Table 2—*Patients With CVID With Bronchial and Parenchymal Abnormalities Identified by CT Scan and MRI*

Abnormality	CT Scan	MRI
Bronchial abnormalities		
Bronchial wall thickening	12 (57.1)	10 (47.6)
Bronchiectasis	11 (52.4)	9 (42.8)
Mucus plugging	9 (42.8)	8 (38.1)
Involvement of bronchial generations up to the fifth and distal	15 (71.4)	11 (52.4)
Parenchymal abnormalities		
Emphysema	7 (33.3)	7 (33.3)
Nodules	12 (57.1)	10 (47.6)
Consolidation	8 (38.1)	8 (38.1)
Abscesses	1 (4.8)	1 (4.8)
Bullae	1 (4.8)	0

Data are presented as No. (%). See Table 1 legend for expansion of abbreviation.

Materials and Methods

Patient Population

Between May 2009 and January 2011, 21 consecutive patients with CVID (17 men, four women, mean age 41 ± 5 years, range 15-69 years) were included in the study. The diagnosis was based on the European Society for Immunodeficiencies/Pan-American Group for Immunodeficiency definition.[14] The mean age at diagnosis was 21 ± 23 years. All patients were followed up and treated with immunoglobulin replacement therapy according to the Italian national guidelines (www.aieop.org). Relevant clinical and immunologic data and pulmonary function tests at the time of the study are described in Table 1.[15] All subjects were evaluated with a low-dose chest CT scan and with MRI study on the same day. Two patients were mild smokers. All participants provided written informed consent, and the study was approved by the institutional review board at Sapienza University of Rome.

MRI Protocol

Chest MRI studies were performed on a 1.5 Tesla imager (Magnetom Avanto; Siemens; Enlargen, Germany) and included a respiratory-triggered T2-weighted rotating blade-like k-space covering (BLADE) sequence (time repetition, 2,000; echo train = 27; field of view, 400 mm; flip angle, 150; slice thickness: 5 mm) acquired on axial and coronal planes. The technical features of this sequence have been described in detail in previous studies.[15,16]

Scan time depended on the respiratory status and size of the patient, ranging between 7 and 16 min (mean, 13 min).

CT Examination

CT images were acquired with a 64-detector row spiral CT scanner (Volume Sensation Cardiac; Siemens), without injection of IV contrast agent, from the lung apices to the upper abdomen in a single breath-hold at the end of full inspiration. The parameters used for acquisition were as follows: 100 kV, CAREdose (Siemens) with quality reference set at 100 mAs; collimation, 64 × 0.6 mm; gantry rotation time, 0.33 s; scan time, 6 s; reconstruction kernel, B30 (for mediastinal evaluation) and B60 (for lung parenchyma evaluation). Dose length product (calculated in mGy × cm) and effective dose (calculated in mSv) were recorded for each examination.

Evaluation of Lung Abnormalities on MRI and CT Scan

Anonymous MRI and CT scan studies were scored in a random order by two independent observers in consensus, adopting a previously validated CT scan scoring system for lung alterations (Bhalla scoring system)[17]; type, severity, and extent of nine radiologic findings were assessed: five related to bronchial pathology (bronchiectasis extension, bronchial wall thickening, bronchiectasis severity, mucus plugging, bronchial generations involved) and four related to parenchymal abnormalities (sacculations or abscesses, consolidations, bullae, emphysema). An extra category was introduced for the assessment of nodules. Nodules were scored according to their number (score = 0, no nodules detected; score = 1, < 5 nodules detected; score = 2, > 5 nodules detected) and size: (score = 1, < 1 cm; score = 2, > 1 cm). Dimension of nodules was scored as the most common nodule dimension detected on both lungs (e-Table 1).

Statistical Analysis

Parametric and nonparametric data are presented as mean ± SD or range, as indicated. For comparison of changes between methods, the Student *t* test and Mann-Whitney test were used for parametric or nonparametric data sets. A *P* value of < .05 was taken as the threshold of statistical significance.

Results

CT Scan and MRI Acquisition

All CT scan and MRI studies were acquired with no complications for all patients. Mean room time for

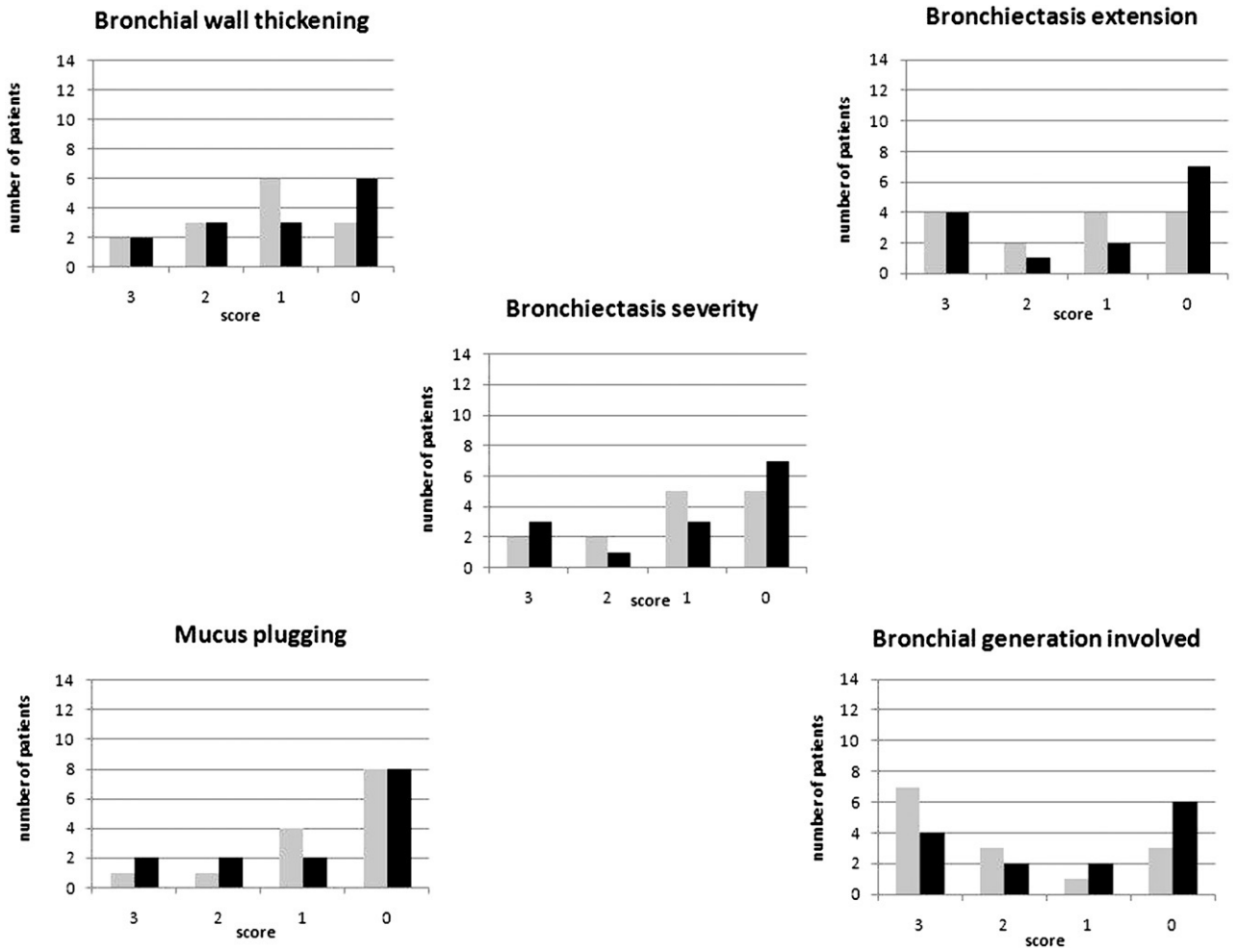

Figure 1. Number of patients with common variable immunodeficiency with a defined bronchial abnormality score (bronchiectasis extension, bronchial wall thickening, bronchiectasis severity, mucus plugging, number of bronchial generations involved) identified by CT scan and MRI. Gray bars refer to MRI data; black bars refer to CT scan data.

CT scan was 4 ± 2 min. Average ± SD dose length product was 106 ± 21 mGy × cm; effective dose was 1.5 ± 0.5 mSv. Mean room time for MRI study was 21 ± 3 min.

MRI and CT Scan in the Evaluation of Lung Abnormalities

MRI was compared with chest CT scan on a cohort of 21 patients with CVID for the identification of morphologic abnormalities. We adopted a previously validated CT scan scoring system,[17] adding an extra category represented by nodules (scored by number and dimensions). Overall, the evaluation of lung abnormalities demonstrated that 71% of patients had bronchial and/or parenchymal abnormalities identified by CT scan and MRI; 23% of patients had bronchial and/or parenchymal abnormalities identified by CT scan only, and two patients had no lung alterations.

Bronchial Abnormalities

The most common lung alterations already reported in patients with CVID were bronchial abnormalities.[2] We confirmed that bronchial wall thickening, bronchiectasis, and mucus plugging were frequent findings (Table 2). These abnormalities were scored according to their severity. We had comparable results between CT scan and MRI in detecting bronchiectasis severity and extension in those patients who had high and moderate grade of bronchial pathology (Fig 1). MRI performance was weaker in detecting mild abnormalities, identified in five patients by CT scan only. A low concordance was found between MRI and CT scan in the assessment of the number of bronchial generations involved: CT scan scores demonstrated a better identification of peripheral airways abnormalities, reporting an involvement of bronchial generations up to the fifth and distal (scores 2 and 3) in 66.6% of the cases. These abnormalities were identified in 38.1% of patients by MRI (Tables 2, 3).

Parenchymal Abnormalities

Parenchymal abnormalities were identified and scored according to their extension. CT scan and MRI gave similar results in detecting the presence and extension of consolidation, abscesses, and emphysema, with overlapping degrees of severity (Fig 2, Tables 2, 4). Abscesses and bullae were rarely reported. The extra category represented by nodules was relevant in our evaluation: Nodules were reported in 12 patients (57.1%) by CT scan and 10 patients (47.6%) by MRI. Nodule dimension was similarly scored with the exception of the two patients who had nodules < 1 cm identified by CT scan only. Nodules presented a maximum transversal diameter ranging between 3 and 17 mm. Figure 3 shows CT scan and MRI images of peripheral bronchial wall thickening;

Table 3—*Bronchial Abnormalities*

	Bronchial Wall Thickening		Bronchiectasis Extension		Bronchiectasis Severity		Mucus Plugging		Bronchial Generation Involved	
Patient	CT Scan	MRI	CT Scan	MRI	CT Scan	MRI	CT Scan	MRI	CT Scan	MRI
1	0	0	0	0	0	0	0	0	0	0
2	3	3	2	2	3	3	1	2	3	3
3	2	2	3	3	1	2	1	2	2	2
4	1	0	1	1	1	1	0	0	2	1
5	1	1	1	1	2	3	2	2	2	1
6	2	2	3	3	1	1	0	0	3	3
7	0	0	1	0	1	0	0	0	3	0
8	1	0	1	0	0	0	0	0	3	0
9	3	3	3	3	3	3	3	3	3	3
10	1	1	1	0	1	0	0	0	1	0
11	0	0	0	0	0	0	0	0	0	0
12	1	1	0	0	0	0	1	1	2	2
13	2	2	3	3	2	1	1	1	3	3
14	1	1	2	1	1	1	0	0	3	1
15	0	0	0	0	0	0	0	0	0	0
16	1	1	2	2	3	3	2	1	3	3
17	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	1	0	3	0
21	0	0	0	0	0	0	1	1	2	2

Morphologic MRI and CT scan studies scored in a random order by two independent observers in consensus, adopting a validated CT scan scoring system for lung alterations (Bhalla scoring system).[17]

CT scan and MRI images of diffuse lung disease with bronchiectasis, bronchial wall thickening, and peripheral nodule; and CT scan and MRI images of bronchiectasis and mucus plugging localized in the right upper region in three patients with CVID.

Discussion

Frequent pulmonary infections are the main CVID-associated comorbidities leading over time to chronic lung disease.[1] Bronchial airways and parenchyma are affected with a wide spectrum of permanent alterations, which can show different degrees of severity.[2] We have recently demonstrated in a large multicenter prospective cohort study that despite immunoglobulin replacement therapy, pneumonia episodes still occur with an estimated incidence of 0.10 episodes/patient/y. Of more concern is the progression of lung disease occurring in about one-half of patients with CVID. Bronchiectasis was the major risk factor identified for pneumonia.[18] Moreover, the analysis of BAL samples of patients with CVID with bronchiectasis showed that the ongoing pulmonary damage may also be due to subclinical infections.[19] Therefore, repeated imaging assessments over time by chest CT scan are required

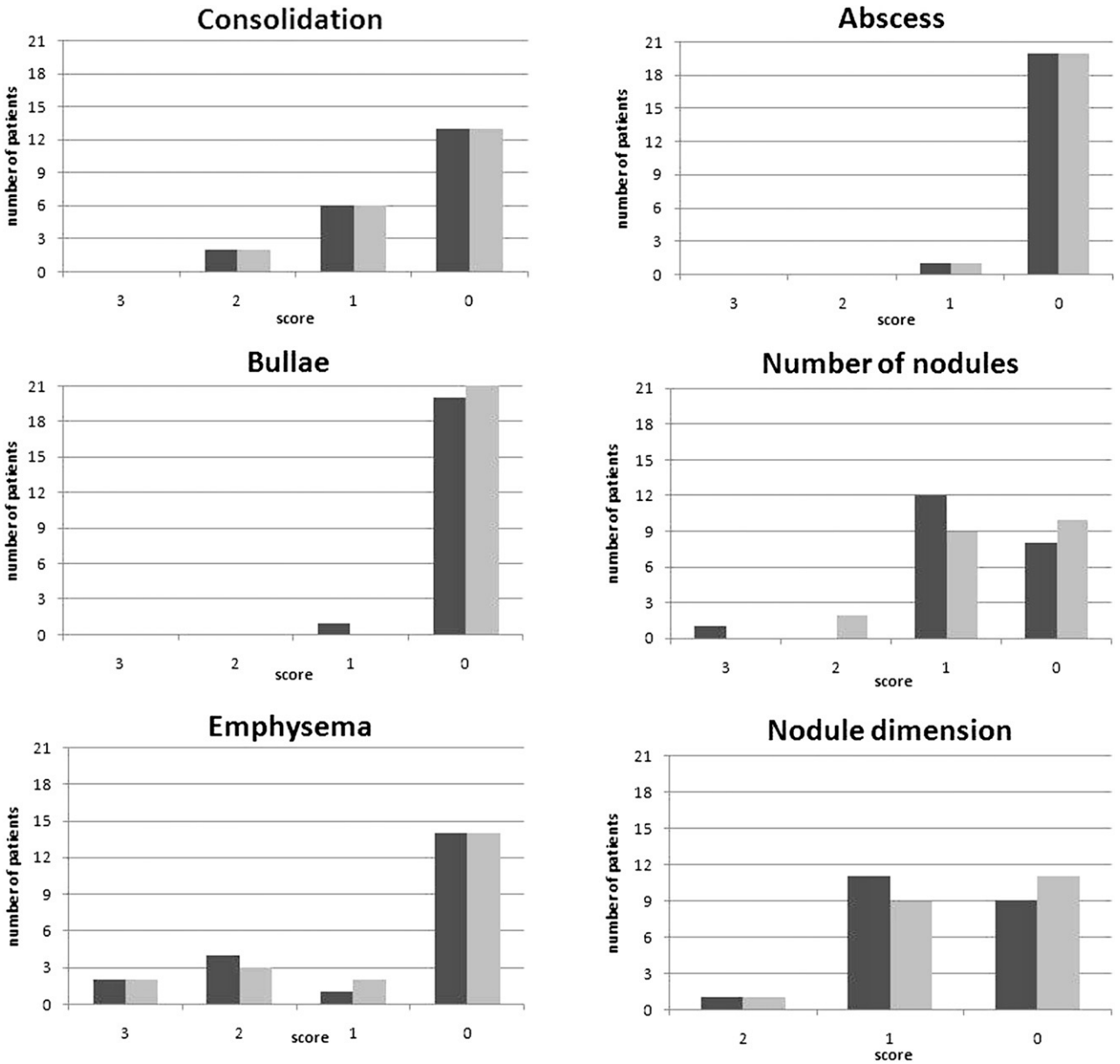

Figure 2. Number of patients with common variable immunodeficiency with a defined parenchymal abnormality score (abscesses, consolidations, bullae, emphysema, nodules number, and dimension) identified by CT scan and MRI. Gray bars refer to MRI data; black bars refer to CT scan data.

Table 4—*Parenchymal Abnormalities*

Patient	Emphysema		Consolidations		Abscesses		Bullae		Number of Nodules		Nodules Dimension	
	CT Scan	MRI	CT Scan	MRI	CT Scan	MRI	CT Scan	MRI	CT Scan	MRI	CT Scan	MRI
1	0	0	0	0	0	0	0	0	0	0	0	0
2	2	2	2	2	0	0	0	0	1	1	1	1
3	1	1	1	1	1	1	0	0	1	2	1	1
4	0	0	0	0	0	0	0	0	1	1	0	0
5	2	2	0	0	0	0	0	0	0	0	0	0
6	2	2	0	0	0	0	0	0	1	1	1	1
7	0	0	0	0	0	0	0	0	0	0	0	0
8	3	3	0	0	0	0	0	0	1	1	1	1
9	3	3	0	0	0	0	0	0	1	1	1	1
10	0	0	0	0	0	0	0	0	1	1	1	1
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	3	2	2	2
13	2	1	2	2	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	1	1	0	0	0	0	1	1	1	1
16	0	0	1	1	0	0	0	1	1	1	1	1
17	0	0	1	1	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	1	0	1	0
19	0	0	1	1	0	0	0	0	0	0	0	0
20	0	0	1	1	0	0	0	0	1	0	1	0
21	0	0	0	0	0	0	0	0	1	1	1	1

Morphologic MRI and CT scan studies scored in a random order by two independent observers in consensus, adopting a validated CT scan scoring system for lung alterations (Bhalla scoring system).[17] The extra category represented by nodules (number and dimension) has been added to the scoring system.

for the diagnosis of acute and chronic respiratory comorbidities. However, an increased radiosensitivity has been described in patients affected by many primary immunodeficiencies, such as ataxia teleangiectasia[20] and CVID. These patients have a increased risk of lymphoproliferative diseases and gastric cancer[1,21,22] and a higher incidence of chromosomal aberrations after x-ray irradiation compared with healthy control subjects.[6-8] Moreover, some primary immunodeficiencies, including CVID, have been explained by defects in DNA repair pathways.[23] Therefore, patients with CVID should be protected from diagnostic and therapeutic procedures using ionizing radiation. Chest MRI was proposed as a potential alternative for the study of the lungs in the late 1980s.[24] Even though spatial resolution is still lower than CT scan, lung MRI is totally radiation-free and also offers the advantages of better tissue characterization and the possibility of performing functional studies.[25]

Similarly to other published studies,[10-13] we analyzed the possibility of comparing MRI to chest CT scan findings in a cohort of patients with CVID. We adopted a previously validated CT scan scoring system,[17] adding an extra category represented by nodules. The need for a validated CT scan scoring system to grade lung abnormalities in patients affected by primary immunodeficiencies has been recently outlined.[26,27] We reported comparable results in the scoring of bronchial and parenchymal abnormalities between morphologic CT scan and MRI. The concordance between the two techniques was good in patients who had severe and moderate degrees of defects. However, MRI was less sensitive in detecting mild bronchial alterations. This was mainly due to the low MRI sensitivity in the assessment of peripheral bronchial alterations, which can be explained by the loss of signal in the peripheral areas of lung parenchyma, as discussed in previous studies performed on other lung diseases, such as cystic fibrosis.[28]

Different MRI protocols have been proposed to evaluate lung parenchyma,[29,30] with the rationale to obtain a compromise between the rapid decay of signal intensity of lung parenchyma and the susceptibility effects induced by endoalveolar gas; shorter echo times (in gradient-echo sequences) or shorter echo spacing (in turbo spin echo sequences) have been suggested to overcome these technical constrains. More recently, half-Fourier-acquired single-shot turbo spin echo sequences have been proposed by various authors, yielding high-quality images with fewer artifacts. Short echo spacing makes this pulse sequence relatively resistant to the inhomogeneous magnetic susceptibility of lung parenchyma, whereas the short acquisition time compensates respiratory and cardiac motion.

Even if in our institution the standard routine protocol for pulmonary MRI includes several of the previously mentioned sequences (T2 half-Fourier-acquired

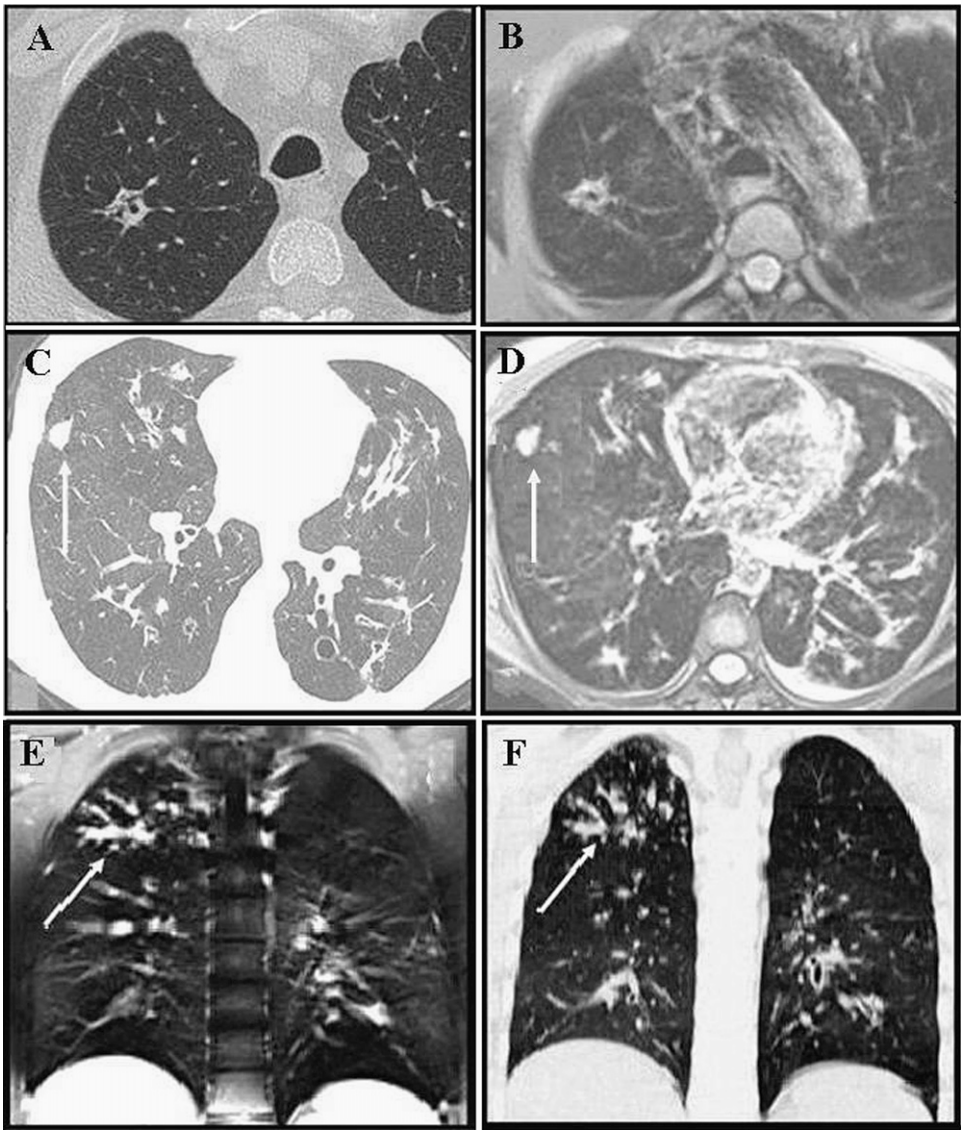

FIGURE 3. A, CT image of peripheral bronchial wall thickening in a patient with common variable immunodeficiency (CVID). B, MRI image of peripheral bronchial wall thickening in a patient with CVID. C, CT image of diffuse lung disease in a patient with bronchiectasis, bronchial wall thickening, and peripheral nodule (arrow). D, MRI image of diffuse lung disease in a patient with bronchiectasis, bronchial wall thickening, and peripheral nodule (arrow). E, MRI image from a patient with bronchiectasis and mucus plugging localized in the right upper region (arrow). F, CT image from a patient with bronchiectasis and mucus plugging localized in the right upper region (arrow).

single-shot turbo spin echo; T1 volume interpolated gradient recalled echo precontrast and postcontrast administration), in our study we chose to use only a dedicated BLADE sequence for morphologic imaging. We needed to select a single morphologic sequence on which to apply our scoring system: a score derived from the assessment of more image data sets—acquired with different parameters—would have affected the reproducibility of the evaluation. No previous studies have been reported on the application of BLADE sequences in the evaluation of the lung. On the basis of previous international studies performed on brain and abdominal imaging and our experience, the BLADE sequence seemed to be most accurate and reproducible for a comprehensive assessment of parenchymal and bronchial pathology, for several reasons: (1) It is a respiratory-triggered sequence showing few breathing artifacts; (2) it has a radial readout of the k-space, which results in much sharper images even if the patient is moving; and (3) it is a slightly longer compared with breath-hold imaging, but may allow the avoidance of scan repetition in uncooperative patients.[31,32] All MRI studies were acquired with the application of a navigator for respiratory triggering. This method was chosen to achieve a further reduction of movement artifacts

related to respiratory activity in less cooperative patients who were not able to maintain an adequate apnea with the application of breath-hold imaging. Because of the application of a navigator for respiratory triggering, all MRI studies were acquired in an expiratory phase, whereas all CT scans were obtained at the end of full inspiration; this did not represent an issue, since the assessment of all morphologic alterations included in our scoring system was not influenced by the respiratory phase adopted. Previous studies of cystic fibrosis lung disease reported that the evaluation of inspiratory and expiratory CT scans match closely.[33]

In conclusion, MRI represents a promising radiation-free technique to evaluate lung alterations in patients with higher radiation sensitivity, such as patients with CVID. CT scan remains the gold standard for diagnosing initial changes in the course of bronchial pathology; MRI can have a relevant role in patients with CVID with a moderate or high degree of structural lung abnormalities. Even with the limits of low spatial resolution, high costs, and low availability, we propose MRI as a possible radiation-free alternative to CT scanning in patients with CVID. Further studies on larger groups of patients are needed to improve image quality and for a definitive standardization of the acquisition protocol.

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Dr Milito: contributed to performing the research; collecting and analyzing the data; and writing, revision, review, and approval of the manuscript.
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