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Increased frequency of cystic fibrosis ΔF508 mutation in bronchiectasis associated with rheumatoid arthritis

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ABSTRACT: This study investigated the clinical characteristics and the possible involvement of the cystic fibrosis transmembrane conductance regulator (CFTR) gene in patients with symptomatic diffuse bronchiectasis (DB) associated with rheumatoid arthritis (RA).

Twenty-six patients with both RA and DB (group RA+DB) and control groups of 29 consecutive patients with RA but no bronchiectasis (group RA) and 29 patients with symptomatic DB of unknown origin (group DB) were prospectively studied.

Among the patients of the RA+DB group, four (15.4%) were heterozygous for the CFTR gene ΔF508 mutation, whereas no ΔF508 mutation was found in patients of the RA and the DB groups (both, $p<0.05$). This frequency of ΔF508 mutation was also higher than the expected frequency (2.8%) in the general European population ($p<0.04$). Sweat chloride values and nasal potential differences were normal in three out of four patients carrying the ΔF508 mutation. In the RA+DB group, those with ΔF508 mutation had more frequent chronic sinusitis ($p<0.05$), a trend toward a more severe pulmonary involvement, and a lower value of nasal potential differences ($p<0.01$) whereas their rheumatic features had no particularity. In the RA+DB group, patients with adult-onset bronchiectasis (including two with ΔF508 mutation) had a greater reduction in total lung capacity ($p<0.05$) and lower nasal potential differences ($p<0.005$) than those with childhood-onset bronchiectasis.

This study suggests a possible deleterious effect of the cystic fibrosis transmembrane conductance regulator mutated protein in the airways which may predispose to the development and severity of bronchiectasis in patients suffering from rheumatoid arthritis.

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Diffuse bronchiectasis (DB) is a condition characterized by a permanent and irreversible dilatation of the bronchi resulting from any of several disorders affecting the airway wall defence mechanisms. The association between DB and rheumatoid arthritis (RA) has been described since the 1940s [1–8]. The prevalence of bronchiectasis in patients with RA has been estimated at between 0.6–3.1% [6, 7, 9], which is 10-fold higher than in a control group of patients with osteoarthritis [7], and higher than the estimated prevalence of 0.13% in Europe [10]. Furthermore, recent prospective studies with high resolution computed tomography (HRCT) of the lungs in patients with RA revealed bronchiectasis in 5.6–30% of the cases [11–16]. Among patients with bronchiectasis, the reported prevalence of RA was 5.2% [8]. These studies suggest more than a chance association between the two diseases, and that bronchiectasis may be a particular feature of RA. More aggressive polyarthritis and a trend toward more severe alterations of pulmonary function tests have been reported in patients with RA and subsequent symptoms of bronchiectasis as compared to those with childhood-onset bronchiectasis [6]. However, no predisposing factor was identified for the development and the severity of bronchiectasis in patients with RA.

The cystic fibrosis transmembrane conductance regulator (CFTR) gene is responsible for cystic fibrosis (CF) [17, 18], which is an autosomal recessive disease characterized by multiple organ involvement including respiratory insufficiency owing to DB associated with severe bacterial airway infection and chronic colonization of the airways by *Pseudomonas aeruginosa*. In Western Europe, 70% of the CF chromosomes carry the ΔF508 mutation [19], whereas the mutation is present in only 2.8% of the general population [20, 21].

The clinical characteristics of patients suffering from both RA and symptomatic DB were examined and the results analysed in the subgroups of patients with childhood- or adult-onset bronchiectasis. CFTR gene mutations were prospectively searched for in these patients to determine whether the CFTR gene might affect the development and the severity of the airway involvement.

Patients and methods

Patient selection

Three groups of Caucasian patients were studied. One group of 26 patients with both RA and symptomatic DB (group RA+DB) was prospectively studied. The patients fulfilled the American Rheumatism Association (ARA) criteria for the classification of RA [22]. The diagnosis of DB, suspected from symptoms such as cough, purulent sputum, haemoptysis, and recurrent or persistent focal infiltrates on chest radiographs, was confirmed in all cases by two independent observers finding evidence of diffuse (more than one lobe) bronchiectasis on HRCT. Patients with a previously identified cause of bronchiectasis such as history of diffuse pulmonary tuberculosis or diffuse interstitial pulmonary fibrosis (traction bronchiectasis) were excluded from the study.

To serve as the control groups for the frequency of mutations of the CFTR gene, deoxyribonucleic acid (DNA) analysis was performed in one group of 29 rheumatoid patients without bronchiectasis fulfilling the ARA criteria [22] (group RA), and in one group of 29 patients with symptomatic DB of unknown origin (following the same inclusion criteria as the RA+DB group) but without joint disease or sicca syndrome (group DB). The RA group was consecutively selected from patients with RA presenting to the Rheumatology department during the study period. These patients had either no pulmonary symptoms and a normal chest radiograph or no evidence of bronchiectasis on HRCT. The DB group was recruited during the same study period among patients who were referred to the Pulmonary Medicine department for respiratory symptoms which led to the diagnosis of DB, in all cases confirmed by HRCT.

Evaluation of rheumatoid arthritis and diffuse bronchiectasis

Evaluation of rheumatoid arthritis. The features of RA recorded included: the duration of RA prior to respiratory symptoms, the presence or absence of Sjögren′s syndrome and of other extra-articular involvement, the number of joint replacement operations or arthrodesis, and the presence (including titres) or absence of rheumatoid factor, antinuclear antibody, and anti-Ro antibody. The functional class (I–IV) was scored according to the criteria of STEINBROCKER *et al.* [23], and all joint radiographs were analysed according to the American College of Rheumatology radiographic classification (I–IV) of progression of RA. Sjögren′s syndrome was diagnosed according to the European Cooperative Study Group preliminary criteria [24]. Human leukocyte antigen (HLA)-DRB1 alleles were characterized by polymerase chain reaction (PCR) amplification (Innolipa, Innogenetics, Gent, Belgium and Dynal A.S., Oslo, Norway).

Evaluation of bronchiectasis and respiratory involvement. Data concerning clinical presentation were recorded. Risk factors for bronchiectasis systematically studied in the RA+DB group included tuberculosis exposure, childhood pneumonia, and family history of bronchiectasis and CF. Total serum immunoglobulin, immunoglobulin (Ig)G, IgA, IgM and IgG subfractions, and α_1-antitrypsin concentrations were determined. Nasal mucociliary clearance was assessed by saccharin transit to detect an immotile ciliary syndrome [25, 26]. Lung function tests were performed and the values for vital capacity (VC), forced expiratory volume in one second (FEV_1), total lung capacity (TLC), and arterial blood gases at rest were measured. The percentage of loss in TLC and in FEV_1 per year since the onset of bronchiectasis symptoms were estimated as (100-TLC % of predicted)/duration of bronchiectasis, and (100-FEV_1 % pred)/duration of bronchiectasis, respectively. Chronic sinusitis with or without polyps were recorded.

This group of patients was also analysed according to the onset of symptoms of bronchiectasis which allowed the definition of two subgroups of patients with childhood- and adult-onset bronchiectasis.

DNA analysis for CFTR mutation

Peripheral blood samples were collected from the patients in the RA+DB, RA and DB groups, and genomic DNA was extracted by standard methods. Twenty exons of the CFTR gene and the surrounding intronic sequences were analysed by denaturing gradient gel electrophoresis, as described previously [27, 28]. Computer analysis was performed using Melt 87, generously provided by L. Lerman (Massachusetts Institute of Technology, Boston, MA, USA). PCR products that displayed an altered mobility in the gel were subsequently sequenced. The sequences of PCR products were determined directly by the Sanger dideoxy-mediated chain-termination method with Sequenase version 2.0 (United State Biochemical, Cleveland, Ohio, USA) [29]. This screening strategy detects ~92% of the CFTR gene mutations in the present population [27]. The variable IVS (InterVening Sequence) 8-poly-T-stretch was analysed as described by CHILLÒN *et al.* [30].

Assessment of sweat chloride concentrations and nasal potential differences

Sweat chloride concentrations and nasal potential differences, which reflect CFTR protein function and are abnormal in CF, were evaluated in patients of the RA+DB group. Sweat chloride concentrations were assessed by pilocarpine iontophoresis and sweat conductivity (Wescor, Logan, UT, AH, USA). Sweat chloride concentrations are defined as abnormal at ≥ 90 mmol·L^{-1} [31]. Nasal potential differences were measured as described previously [32] and were expressed as the mean value of both nostrils. In three patients, it was not possible to determine the nasal potential differences with confidence because of chronic use of an endonasal oxygen tube which renders this measurement unreliable. In the authors′ laboratory, values < -30 mV are found in patients with CF.

Statistical analysis

The Student′s t-test or Mann–Whitney U-test were used for two-by-two comparisons between groups for parametric and nonparametric variables, respectively. The Chi-squared method (Fisher′s exact p-value) was used for comparisons of frequency.

Table 1. – Clinical characteristics of the three groups of patients

	RA+DB	DB	RA
Subjects n	26	29	29
Age yrs	59 (37–71)	46 (25–82)	62 (28–89)
Sex F/M	23/3	17/12	22/7
P_{a,O_2} mmHg	73±11	75±10	
P_{a,CO_2} mmHg	39±4	40±4	
TLC % pred	90±17	87±18	
FEV1 % pred	68±22	72±10	

Results are expressed as mean±SD or as median (range). RA+DB: rheumatoid arthritis with diffuse bronchiectasis group; DB: diffuse bronchiectasis group; RA: rheumatoid arthritis and no bronchiectasis group; F: female; M: male; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; TLC: total lung capacity; FEV1: forced expiratory volume in one second. Comparisons between groups are not significant. (1 mmHg=0.133 kPa.)

Results

The clinical characteristics of the patients in all three groups are summarized in table 1.

Characteristics of patients with RA associated with DB

Twenty-six patients (23 females and three males, median age 59.0 yrs range 35–71 yrs) were included in the RA+DB group.

Characteristics of rheumatoid arthritis in the group as a whole. The main RA features of the 26 patients are listed in table 2. Eight (31%) patients were affected by Sjögren's syndrome, five (19%) had rheumatoid nodules, one (4%) had myositis, but no other extra-articular involvement was detected. Most of the patients (15/26) had severe (stage III or lV) radiographic abnormality of the joints and 10/26 patients were severely (class III or IV) affected functionally. They had received a mean of 4.2 types of different disease-modifying antirheumatic drugs (such as methotrexate, gold salts, sulphasalazopyrine, penicillamine or hydroxychloroquine) and 69% of them were on long-term low dose corticosteroid therapy. Among the 26 patients, 10 (38%) had received methylprednisolone pulses and 12 (46%) had been treated with methotrexate, six (23%) of whom had been taking the treatment for a mean duration of 4 yrs at the time of the study. No side-effects were reported despite careful follow-up. Fifteen patients have been treated with penicillamine, 13 of whom had a long history of pulmonary symptoms that preceeded the onset of the treatment. They had a mean of 1.5 joint replacement or arthrodesis operations per patient and 12 (46%) had at least one joint replacement or arthrodesis. Twenty-three (88%) patients were rheumatoid factor-positive and four (15%) patients had a low titre of antinuclear antibodies.

Table 2. – Characteristics of the 26 patients with rheumatoid arthritis and diffuse bronchiectasis

			Characteristics of rheumatoid arthritis					Characteristics of bronchiectasis					
Pt. No.	Sex	Age yrs	Age at onset yrs	Sjögren's syndrome	Func. class	Rx grade	HLA-DRB1*	Age at onset yrs	FEV1 % pred.	Bacteria isolated from sputum	Sweat chloride concen. mmol·L^{-1}	NPD mV	CFTR gene mutation
1	F	67	51	Yes	II	II	0401/1401	51	20	*P. aeruginosa*	48	-24	ΔF508/-
2†	F	52	29	Yes	IV	IV	0406/0416	35	50	*P. aeruginosa*	ND	-31	ΔF508/-
3	F	35	16		II	II	0311/1302	4	82	*H. influenzae*	18	-21	ΔF508/-
4	F	52	42		II	II	03011/1001	4	79	ND	55	-21.0	ΔF508/-
5	F	56	48		II	III	0101/0401	12	90	Normal flora	40	-15.3	R668C/-
6	F	59	49		III	III	0401/0405	4	14	*P. aeruginosa*	57	ND	S1235R/-
7	F	55	53		II	I	0101/1001	2	92	Normal flora	42	-17.3	-/-
8	F	55	46		III	III	0101/1302	3	83	Normal flora	60	-18.7	-/-
9†	F	66	20		III	IV	0101/0401	4	78	*P. mirabilis*	35	-15.8	-/-
10	M	71	61		II	III	0701/1001	67	60	Normal flora	34	-19.2	V562I/-
11	M	59	34		II	III	0101/0408	53	94	*H. influenzae*	62	-20.8	-/-
12	F	56	30	Yes	III	III	0101/0311	10	89	Normal flora	53	-11.1	-/-
13	F	46	43	Yes	II	III	0101/0405	9	73	*H. influenzae*	29	-21.3	-/-
14	F	47	41		II	III	03011/0401	9	80	Normal flora	86	-16.5	-/-
15	F	54	44		II	II	0401/0401	1	67	Normal flora	50	-13	-/-
16	F	59	37		III	III	0101/0401	3	53	*H. influenzae*	70	-16.8	-/-
17	F	49	47		I	I	03011/1401	10	58	*H. parainfluenzae*	79	-18.5	-/-
18†	F	65	37	Yes	III	III	03011/1501	56	43	Normal flora	35	-33.8	-/-
19	F	65	54	Yes	II	III	0101/1101	10	91	ND	64	-9.6	-/-
20	F	70	55		III	III	0101/0401	4	80	Normal flora	38	-13.5	-/-
21	F	69	53		IV	IV	0101/1501	4	35	*P. aeruginosa*	35	ND	-/-
22	M	66	63		II	II	0401/1104	63	97	Normal flora	36	-20.2	-/-
23	F	61	56		I	I	03011/0701	4	76	*Flavobacterium* spp.	32	-15.9	-/-
24	F	60	27	Yes	I	II	03011/1501	4	63	*H. influenzae*	67	-18.1	-/-
25†	F	70	68		III	II	0405/0416	13	56	*B. catarrhalis*	59	ND	-/-
26	F	57	55	Yes	I	I	0701/1501	8	57	*H. influenzae*	50	-18	-/-

Pt.: patient; Func.: functional; Func. class: characterized according to the criteria of STEINBROCKER *et al.* [22]; Rx grade: American Rheumatism Association radiological stage; HLA: human leukocyte antigen; FEV1: forced expiratory volume in one second; NPD: nasal potential differences; CFTR: cystic fibrosis transmembrane conductance regulator; F: female; M: male; *P. aeruginosa*: *Pseudomonas aeruginosa*; *H. influenzae*: *Haemophilus influenzae*; ND: not done; *P. mirabilis*: *Proteus mirabilis*; *H. parainfluenzae*: *Haemophilus influenzae*; *B. catarrhalis*: *Branhamella catarrhalis*. †: deceased.

The results of DRB1 typing are shown in table 2. Nine (35%) patients had two copies of DRB1 alleles known to encode the RA-associated DRB1 "shared epitopes" amino acid sequence (DRB1*0101, *0102, *0401, *0404, *0405, *0408, *1001, *1402) and 11 (42%) one copy. The DRB1 *0401 allele was present in 10 (38%) patients.

Characteristics of pulmonary involvement in the group as a whole. Study of risk factors for diffuse bronchiectasis. None of the patients had a family history of CF. A family history of DB was found in three cases, one of which also had associated RA. No hypogammaglobulinaemia, IgG, IgA or IgM deficiencies were detected, and the levels of IgG_1, IgG_2, IgG_3, and α_1-antitrypsin were within normal ranges in all the patients with RA and DB. The nasal mucociliary clearance was normal (<20 min) in all subjects.

Pulmonary function. The results of pulmonary function tests are shown in tables 1, 2 and 3. Most of the patients (13/26) had an obstructive lung disorder, defined as a low FEV1 (<80% pred) and FEV1/VC (<70% pred) with a normal or high TLC. Restrictive lung disorders, defined as low TLC (<80% pred) and a normal FEV1/VC ratio, were observed in two patients. Combined restrictive and obstructive disorders were seen in six of the 26 patients. The severity of the pulmonary involvement was the main contributor to the death of three of the 26 patients (patients 2, 18, 25).

Bacterial colonization. All patients suffered repeated episodes of bronchitis and/or pneumonia, each requiring several courses of antibiotics varying in number. The most common bacterial isolates from sputum were *Haemophilus influenzae* (6/24) and *P. aeruginosa* (4/24) (table 2).

Comparison between patients with childhood- and adult-onset bronchiectasis. Among the RA+DB group, 20 patients had bronchial symptoms that had been present since childhood (median age 4 yrs, range 1–13 yrs) which preceded the onset of RA (median age 46.5 yrs, range 16–68 yrs). Six patients had adult-onset bronchial symptoms (median age 54.5 yrs; range 35–67 yrs). In this latter group, two patients had respiratory symptoms preceding the onset of arthritis for 1 yr and four had clinical manifestations of bronchiectasis that followed the rheumatological signs with a delay of between 6 and 19 yrs (table 2).

Patients with adult-onset bronchiectasis, which included a larger proportion of males (p<0.005), had a more aggressive arthritis than those with childhood-onset bronchiectasis. The median number of different types of disease-modifying antirheumatic drugs per patient was higher (4.5, range 4–10 *versus* 3.0, range 1–10, respectively; p=0.05). They tended to be more frequently on long-term low dose corticosteroid therapy (100 *versus* 60%, respectively; p=0.13). They also had a greater alteration in pulmonary function which was significant for TLC (p<0.05) and the estimated loss in TLC and FEV1 per year of duration of symptoms of bronchiectasis (both p<0.0001) (table 3).

Nasal potential differences were lower in patients with adult-onset than childhood-onset bronchiectasis (p<0.005) (table 3). Sweat chloride concentrations did not differ between these two subsets of patients (p>0.20).

CFTR gene analysis

Analysis of CFTR gene mutations. Among the 26 patients in the RA+DB group, four (15.4%) were heterozygous for the ΔF508 mutation (patients 1 to 4) (table 2). In contrast, no ΔF508 mutation was found in the RA group or in the DB group of patients (both, p<0.05) (table 4). This frequency of 15.4% is also significantly higher than the expected frequency (2.8%) of the ΔF508 mutation in the general European Caucasian population [17, 21] (p<0.04) (table 4). No further mutation was detected in the four patients heterozygous for the ΔF508 mutation. In the RA+DB group three other mutations were found (R668C in patient 5, S1235R in patient 6 and V5621 in patient 10). Sweat chloride concentrations were within normal values in all patients in the RA+DB group (table 2). Two patients in this group (patients 14 and 17) had borderline values for sweat chloride concentrations but normal nasal potential differences, and no CFTR gene mutation. Among the four patients with RA and DB carrying the ΔF508 mutation, the nasal potential differences were normal in three and borderline (-31 mV) in one (patient 2). Borderline abnormal nasal potential differences were also observed in one of the patients without a CFTR gene mutation (patient 18).

Table 3. – Pulmonary function tests, nasal potential differences and sweat chloride concentrations in 26 patients with rheumatoid arthritis and diffuse bronchiectasis

	Group as a whole	Childhood-onset bronchiectasis	Adult-onset bronchiectasis
Subjects n	26	20	6
Age yrs	59.0 (35–71)	56.5 (35–70)	65.5 (52–71)
Sex F/M	23/3	20/0	3/3**
P_{a,O_2} mmHg	73.4±11.5	74.5±12.0	69.7±9.8
P_{a,CO_2} mmHg	39.6±4.3	39.7±4.6	39.2±3.5
TLC % pred	89.7±17.0	93.6±15.9	76.8±14.7*
FEV1 % pred	67.7±22.4	69.8±20.0	60.7±30.0
FEV1/FVC %	63.7±15.9	64.6±15.6	60.8±18.1
Nasal potential differences mV	-18.1 (-9.6– -33.8)	-16.8 (-9.6– -21.3)	-22.4 (-19.2– -33.8)**
Sweat chloride concentrations $mmol \cdot L^{-1}$	50 (18–86)	53 (18–86)	36 (34–62)

Results are expressed as mean±SD or as median (range). F: female; M: male; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; TLC: total lung capacity; FEV1: forced expiratory volume in one second; FVC: forced vital capacity. *: p<0.05; **: p<0.01. (1 mmHg=0.133 kPa.)

Table 4. – Frequency of the ΔF508 mutation in the different groups of patients and in the Western European general population

	RA+DB group (n=26)	RA group (n=29)	DB group (n=29)	Western European general population (expected frequency)
ΔF508 mutation				
Patients n	4	0	0	
Patients %	15.4*$^{+\#}$	0	0	2.8

RA+DB: rheumatoid arthritis with diffuse bronchiectasis. *: $p<0.05$ *versus* patients with rheumatoid arthritis and no bronchiectasis (RA group); $^{+}$: $p<0.05$ *versus* patients with diffuse bronchiectasis and no rheumatoid arthritis (DB group); $^{\#}$: $p<0.04$ *versus* Western European general population.

No mutations including the 5T variant were found in the RA group. In the DB group, two patients carried mutations: one was compound heterozygous (G542X/3849+10Kb C→T) and was diagnosed as suffering from an atypical CF with a normal sweat chloride concentration, while the other was heterozygous for the missense mutation G239R with normal values of both sweat chloride concentrations and nasal potential differences. Neither of these two subjects had pancreatic insufficiency.

Comparison between subjects with and without the ΔF508 mutation in the RA+DB group. In the patients with RA and DB, subjects with the ΔF508 mutation (table 5) tended to have a more severe pulmonary involvement which was significant for the mean annual loss in TLC, and an increased frequency of chronic sinusitis with or without polyps (each comparison, $p<0.05$). The subgroup of patients with the ΔF508 mutation also had a lower value of nasal potential differences ($p<0.01$). No differences could be detected concerning either the age of onset of bronchial symptoms or the characteristics of the rheumatic disease (including the age of RA onset, the functional class, the radiological grade, and the treatment regimens).

Discussion

Despite reports of an increased prevalence of bronchiectasis in RA, the relationship between the two diseases is poorly understood. The major finding of the present study is a higher than expected frequency of heterozygous ΔF508 mutation in the patients with both RA and DB whereas no other cause of bronchiectasis was found.

The observed frequency of ΔF508 mutations in patients with both RA and DB is more than five-fold higher than the expected frequency in the general European population. It is also significantly higher than the frequency of the mutation in the control patients with RA but no bronchiectasis, indicating that the ΔF508 mutation is not a marker of RA itself. The wide spectrum of phenotypes in CF makes it difficult to interpret the involvement of the CFTR gene mutations. These mutations may either reveal atypical forms of CF [33] or may have an effect on a disease unrelated to CF. Thus, an increased frequency of CFTR gene mutations has been reported in patients with DB [34–37]. To exclude an atypical form of CF requires a complete analysis of the CFTR gene and a study of the CFTR protein function by measurement of sweat chloride concentrations and/or nasal potential differences. Only two of the four studies that reported an increased prevalence of CFTR mutations in DB performed these analyses [34, 35]. In one report of 16 patients with DB and normal sweat chloride test values, only one carried the ΔF508 mutation [35]. In another study of 63 patients with DB, the frequency of the ΔF508 mutation was significantly higher than in the general population only in patients with high sweat chloride concentrations who are likely to correspond to atypical CF, and not in patients with normal sweat test results [34]. These studies suggest that, after the exclusion of CF, the ΔF508 mutation *per se* is no more frequent in patients with DB than in the general population. This interpretation is in accordance with the present finding that in the DB group, none of the patients carried the ΔF508 mutation whereas two patients had other CFTR mutations, one of whom was diagnosed as suffering from an atypical form of CF. None of the patients with both RA and DB carrying the ΔF508 mutation had abnormal sweat chloride concentrations. For only one of them with borderline nasal potential differences was the value of sweat chloride concentrations unknown. Twenty exons of the CFTR gene and the surrounding intronic sequences were systematically analysed. No further mutation was detected in the four patients with both RA and DB carrying the ΔF508 deletion. Thus, even though no evidence was found that RA+DB patients with a ΔF508 heterozygote mutation can be classified as having CF, the possibility that these patients or some of them correspond to very atypical or

Table 5. – Pulmonary involvement in subjects with or without the ΔF508 mutation in the group of patients with rheumatoid arthritis and diffuse bronchiectasis

	With ΔF508 (n=4)	Without ΔF508 (n=22)	p-value
Age yrs	52.0 (35–67)	59.0 (46–71)	0.16
Age of onset of bronchiectasis yrs	19.5 (4–51)	8.5 (1–67)	0.66
P_{a,O_2} mmHg	71.5±15.1	73.7±11.1	0.85
P_{a,CO_2} mmHg	40.5±2.4	39.4±4.6	0.22
TLC % pred	77.5±13.5	92.0±16.8	0.09
FEV_1 % pred	57.7±29.0	69.5±21.3	0.40
Estimated annual loss in FEV_1 %	0.77±0.37	0.51±0.35	0.17
Estimated annual loss in TLC %	0.42±0.21	0.13±0.28	0.04
Nasal potential differences mV	-22.5 (-21– -31)	-17.3 (-9.6– -21.3)	0.009
Sweat chloride concentrations $mmol \cdot L^{-1}$	48 (18–55)	50 (32–86)	0.35

Results are expressed as mean±SD or as median (range). For definitions see footnote to table 3.

mild expression of CF cannot be excluded. Nevertheless, however these patients are classified, it is believed that the high frequency of the ΔF508 mutation in RA+DB group patients suggests that this mutation influences the phenotype of RA. Since the frequency of the ΔF508 deletion in the RA+DB group is compared to the lack of a mutation in the RA group, which included populations of rather small sample size, these findings need to be confirmed with larger populations of patients. However, the authors would like to emphasize that this series of 26 patients with DB associated with RA is the largest group studied to date and that several control groups (RA alone, DB alone, and comparison with the general population) were included to prevent any possible bias in the study. In the RA+DB group, in addition to the ΔF508 mutation three other missense mutations were found (patients 5, 6 and 10). The significance of these missense mutations found in the absence of any other detectable mutation is unclear. Although the V562I and S1235R mutations have been described in CF patients, the putative detrimental effect of these mutations is disputable. The R668C mutation was first described as a DNA polymorphism [28]. However, it was also detected in patients with emphysema [35].

Although the number of subjects is low, the presence of the ΔF508 mutation within the RA+DB group seems to be associated with a trend towards a more severe pulmonary outcome which was significant for the mean annual loss in TLC. The frequency of chronic sinusitis with or without polyps was also more frequent in patients with the ΔF508 mutation, whereas airway infections or colonization by *P. aeruginosa* were similar in patients with and without the mutation. However, this mutation does not seem to confer a specificity in the articular involvement. The great majority of these patients presented symptoms associated with bronchiectasis before the onset of arthritis, as in all previous studies [4–8] with the exception of the series reported by SHADICK *et al.* [6]. DB was responsible for obstructive and/or restrictive respiratory disease and was associated with frequent airway infections. The presence of DB appeared to be associated with a worse general outcome of the disease. During the study period, respiratory disease was responsible for three out of the four deaths. Respiratory disease has already been reported to be the major cause of death in such patients [6, 38]. Since a previous series by SHADICK *et al.* [6] indicated that patients with adult-onset bronchiectasis had more frequent extra-articular manifestations, more aggressive arthritis, and a trend towards more severe alteration in their pulmonary function, the present study also examined the results in the subgroups of patients with adult- and childhood-onset bronchiectasis. Among patients with RA, these results confirm that those with adult-onset bronchiectasis appear to have a more aggressive arthritis than those with childhood bronchiectasis. The severity of the pulmonary involvement was also more pronounced in patients with adult-onset bronchiectasis. However, it was found that the ΔF508 mutations were observed in both subsets of patients with adult- and childhood-onset bronchiectasis (two patients in each subgroup). Therefore, the presence of this mutation does not give an obvious explanation to the difference in either the onset of bronchial symptoms or in the severity of pulmonary involvement between these two subsets of patients with RA and DB.

The possible role of the CFTR gene in the association of RA and DB and in the particular severity of the pulmonary outcome in patients with the ΔF508 mutation and in the subset of patients with adult-onset bronchiectasis is unclear. Nasal potential differences which reflect ionic transport across the respiratory mucosa are decreased when an altered CFTR protein exists. The potential differences in airway mucosa become less negative with increasing age [39]. The lower values of nasal potential differences in patients with the ΔF508 mutation and in the subset of patients with adult-onset bronchiectasis cannot be explained by differences in age which was similar. Therefore, in addition to the high unexpected frequency of the ΔF508 mutation, the present finding of lower nasal potential differences in patients with the ΔF508 mutation and in patients with adult-onset bronchiectasis, both of which had a more severe pulmonary involvement, suggests that an altered CFTR protein in the airway mucosa may be one of the contributing factors to the genesis and severity of bronchiectasis associated with RA. There is increasing evidence that the CFTR protein may have functions other than the known action on chloride transport, such as the regulation of plasma membrane recycling, bicarbonate conductance, pH, and other channel protein activities [40, 41]. The possibility that the CFTR mutated gene may contribute to other cell dysfunctions involved in RA cannot be excluded.

In conclusion, these results suggest that there is an increased frequency of heterozygous ΔF508 mutation in the cystic fibrosis transmembrane conductance regulator gene among patients with both rheumatoid arthritis and symptomatic bronchiectasis. It is premature to draw conclusions from this finding. However, the mutated cystic fibrosis transmembrane conductance regulator gene may be deleterious in the respiratory tract and may predispose to bronchiectasis subjects suffering from a particular and severe subtype of rheumatoid arthritis. These results should be confirmed by other studies including larger populations of patients with rheumatoid arthritis and bronchiectasis.

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