

Pulmonary abnormalities in patients with primary hypogammaglobulinemia

Leena Kainulainen, MD,^a Matti Varpula, MD,^b Kari Liippo, MD,^c Erkki Svedström, MD,^b Jukka Nikoskelainen, MD,^d and Olli Ruuskanen, MD^a *Turku, Finland*

Background: Pulmonary complications are common in patients with primary hypogammaglobulinemia. Intravenous immunoglobulin replacement therapy has been thought to reduce the occurrence of pulmonary complications, yet they do occur.

Objective: The purpose of this study was to evaluate pulmonary abnormalities in 22 patients with primary hypogammaglobulinemia (18 with common variable immunodeficiency, 4 with X-linked agammaglobulinemia) and to conduct a prospective 3-year follow-up study to assess the possible progression of pulmonary abnormalities.

Methods: Pulmonary changes were evaluated with use of pulmonary imaging (chest radiographs, high-resolution computed tomography), and pulmonary function testing.

Results: High-resolution computed tomography revealed pulmonary abnormalities in 21 patients. Bronchiectasis was present in 16 patients, whereas chest radiographs revealed bronchiectasis in only 3 patients. Pulmonary function testing showed obstruction in 5 patients. A prospective 3-year follow-up was conducted in 14 patients. It showed silent progression of bronchiectasis in 5 of the 14 patients, all of whom were receiving intravenous immunoglobulin replacement therapy and had preinfusion serum IgG concentrations of 5 g/L or more.

Conclusions: Pulmonary abnormalities develop in most patients with primary hypogammaglobulinemia. A new finding is that silent and asymptomatic progression of pulmonary changes may occur in patients despite an adequate immunoglobulin replacement therapy. High-resolution computed tomography is the method of choice in monitoring pulmonary changes. (*J Allergy Clin Immunol* 1999;104:1031-6.)

Key words: Hypogammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, bronchiectasis, high-resolution computed tomography, immunoglobulin replacement therapy

Primary hypogammaglobulinemias are disorders of heterogeneous etiologies, characterized by low levels of

Abbreviations used

CVID:	Common variable immunodeficiency
FVC:	Forced vital capacity
HRCT:	High-resolution computed tomography
IMIG:	Intramuscular immunoglobulin
IVIG:	Intravenous immunoglobulin
MEF ₅₀ :	Maximum expiratory flow at 50% of forced vital capacity
PFT:	Pulmonary function testing
SCIG:	Subcutaneous immunoglobulin
XLA:	X-linked agammaglobulinemia

serum immunoglobulins and impaired antibody responses. Common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA) represent a majority of cases of hypogammaglobulinemia. The patients are prone to respiratory tract infections that often result in pulmonary damage.^{1,2} Parenteral immunoglobulin replacement therapy has reduced the occurrence of severe respiratory tract infections, and it has also been thought to reduce the development of permanent pulmonary damage.³ However, despite the immunoglobulin replacement therapy pulmonary complications do occur.⁴⁻⁸

The purpose of this study was to evaluate pulmonary abnormalities in 22 patients with CVID or XLA by imaging methods and pulmonary function testing. A 3-year prospective follow-up was carried out on 14 patients.

METHODS

Table I presents the patient characteristics. The study group consisted of 22 patients (12 male, 10 female) with CVID or XLA being treated at the Turku University Hospital, Turku, Finland. The median age was 36 years (range 7-69 years). Three of the patients were children, aged 7, 8, and 13 years at the beginning of the study. Eighteen patients were diagnosed as having CVID and 4 as having XLA according to the diagnostic criteria of the World Health Organization Immunodeficiency Group.² The diagnostic criteria of CVID consisted of decreased serum immunoglobulin concentrations (serum IgG <-2 SD of normal values), defective antibody formation,^{9,10} and exclusion of other known causes of humoral immune defects. Patients with XLA were male with very low serum Ig concentrations (serum IgG <2 g/L) and no mature CD19⁺ B lymphocytes in the peripheral blood. In 2 patients with XLA, the gene analysis of Bruton tyrosine kinase was carried out to confirm the XLA diagnosis (Vihinen, Tampere University, Tampere, Finland).

The duration of the symptoms before diagnosis varied from 1 to

From the Departments of Pediatrics,^a Diagnostic Radiology,^b Pulmonary Diseases,^c and Medicine,^d Turku University Hospital, Turku, Finland.

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Reprint requests: L. Kainulainen, MD, Research Unit, Department of Pediatrics, Turku University Hospital, Vähä-Hämeenkatu 1 A 3, 20500 Turku, Finland.

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TABLE I. Patient characteristics

Patient No./sex (y of birth)	Diagnosis	Duration of symptoms before diagnosis (y)	Age at diagnosis (y)	Recurrent respiratory tract infections before diagnosis
1/M (-29)*	CVID	14	54	Pneumonia
2/F (-59)*	CVID	4	22	CMS, pneumonia
3/M (-59)*	CVID	4	34	Sinusitis, pneumonia
4/F (-44)	CVID	2	35	ROM, sinusitis, pneumonia
5/M (-81)*	CVID	<1	1	None
6/F (-35)	CVID	16	46	ROM, CMS, bronchitis
7/F (-43)*	CVID	8	45	Bronchitis
8/F (-86)*	CVID	<1	5	Pneumonia
9/M (-54)*	CVID	1	28	ROM, pneumonia
10/M (-39)*	CVID	25	46	CMS, bronchitis, pneumonia
11/F (-25)*	CVID	4	59	CMS
12/F (-57)*	CVID	10	33	CMS, ROM, bronchitis, pneumonia
13/M (-67)*	CVID	4	24	Pneumonia
14/F (-61)	CVID	3	33	Bronchitis, pneumonia, sinusitis
15/F (-54)	CVID	1	30	Pneumonia
16/F (-40)	CVID	3	33	Pneumonia
17/M (-48)	CVID	10	22	Pneumonia, bronchitis, sinusitis
18/M (-60)	CVID	4	18	Pneumonia, sinusitis, ROM
19/M (-87)*	XLA	<1	1	Pneumonia
20/M (-62)	XLA	5	5	Pneumonia, ROM
21/M (-64)*	XLA	5	5	ROM, pneumonia, bronchitis
22/M (-73)*	XLA	<1	1	None

M, Male; IVIG, intravenous immunoglobulin; F, female; CMS, chronic maxillary sinusitis; ROM, recurrent otitis media; IMIG, intramuscular immunoglobulin; SCIG, subcutaneous immunoglobulin; NA, data not available.

*Participated in the 3-year follow-up study.

25 years (mean 6 years). All patients except one were receiving regular immunoglobulin substitution therapy (15 IVIG, 2 SCIG, and 4 IMIG therapy) every 3 or 4 weeks. Intramuscular treatment was changed to IVIG in 3 patients after their initial visits to our hospital (patients 17, 18, and 22). One patient (patient 16) refused immunoglobulin replacement therapy. The mean duration of immunoglobulin replacement therapy was 10.5 years (Table I). Nineteen patients were nonsmokers and 3 were former smokers. None of the patients had had pulmonary tuberculosis. Patients had had no signs of acute respiratory infections during the 2 months preceding the radiologic studies and during the 2 weeks preceding pulmonary function testing (PFT). None of the patients received prophylactic antibiotic therapy. Two patients in the study group died during the study period: one of renal failure from systemic amyloidosis¹¹ and one from disseminated cytomegalovirus infection.¹²

Chest radiographs (posteroanterior and lateral projections) and high-resolution computed tomography (HRCT) were obtained for 22 patients. The films were evaluated by a radiologist (M. V.) experienced in pulmonary radiology. Both the chest radiographs and the HRCT images were evaluated independently. Finally, a consensus of findings was made by 2 radiologists reviewing the films. All abnormalities, especially the parenchymal and pleural changes, were recorded. Radiologic studies were always carried out before the patients received their immunoglobulin doses, to avoid the ground-glass opacity changes caused by the immunoglobulin infusion. A follow-up-study after 3 years was conducted on 14 patients.

Imaging techniques

The posteroanterior and lateral chest radiograph films were obtained with use of either a conventional film-screen system or a digital imaging system (Fuji FRC 9501, Tokyo, Japan). The high-resolution scans were performed with a CT Pace scanner (General Electric Medical Systems, Milwaukee, Wis). All patients were

scanned supine, from lung apex to diaphragm, with 1-mm sections at 15-mm intervals. The images were obtained at full inspiration with a 2-second data acquisition time at 120 kVp and 130 to 160 mA settings. The images were reconstructed with bone algorithm and targeted at both lungs separately with a field of view of 20 cm. The images were documented on laser film prints with a window level of -600 HU and window width of 1500 HU.

Image analysis

All parenchymal abnormalities such as parenchymal scars, fibrosis-like changes, pleural thickening and bronchiectasis were recorded from the chest radiographs and HRCT images.¹³ In addition, ground-glass opacity, emphysema, bullae, atelectasis, and parenchymal nodules were recorded from HRCT images.¹⁴ The findings were graded from 1 to 3, as mild, moderate, or advanced. Each of the 5 lobes was analyzed separately. The general score of the findings was graded according to the most severe finding and it was upgraded if abnormalities were found from more than 2 lobes.

PFT

PFT was carried out in 15 adult patients (13 with CVID, 2 with XLA). It could be carried out twice in 10 patients with a 2-year interval, in 1995 and 1997. Forced vital capacity (FVC), FEV₁, and maximum expiratory flow at 50% of FVC (MEF₅₀) volume in 1 second were obtained with a Jaeger Masterlab spirometer (Erich Jaeger, Wurzburg, Germany). FEV₁ as a percentage of FVC (FEV₁/FVC) was calculated. Diffusing capacity was measured with use of the standard single-breath carbon monoxide test with the helium dilution method (Jaeger Masterlab). All values were depicted as percentages of predicted values.¹⁵ Obstructive ventilation defect was considered present if the FEV₁/FVC was <80% of the predicted value. Obstruction was graded as mild (<80%) or moder-

At diagnosis	Serum IgG concentrations (g/L)		Replacement therapy	Treatment years at onset of study
	1994	1997		
2.5	9.9	10	IVIG	9
2.8	4.6	6.1	IVIG	9
2.0	4.7	5.4	IVIG	2
0.6	2.4	Died	IMIG	15
1.5	2.6	6.5	IVIG	12
1.3	9.6	Died	IVIG	13
3.9	5.3	6.4	SCIG	6
1.7	3.7	5.1	IVIG	4
1.0	5.3	8.7	IVIG	12
1.2	3.7	4.9	IVIG	10
2.5	3.8	4.5	IVIG	10
2.8	3.3	4.9	IVIG	4
3.5	4.4	4.4	SCIG	4
2.8	2.8	6.4	IVIG	1
5.5	6.2	8	IVIG	1
0.4	NA	2.0	No replacement	—
2.6	NA	5.0	IMIG→IVIG	23
NA	NA	2.2	IMIG→IVIG	16
NA	1.8	8.1	IVIG	6
<1	6.2	NA	IVIG	27
<1	3.1	5.7	IMIG→IVIG	25
<1	8.1	9.2	IVIG	11

ate (<65%). Diffusion capacity was considered to be decreased at <75% of the predicted value. A specialist in lung diseases (K. L.) evaluated the clinical status of the patients.

Patients completed questionnaires at the onset and at the end of the 3-year prospective study concerning respiratory infections (ie, sudden worsening of rhinitis and cough with or without fever), the number of antibiotic treatments, and clinical symptoms (cough, sputum production, exercise tolerance).

Informed consent was obtained from all patients. The study protocol was approved by the Joint Commission on Ethics of Turku University Hospital and University of Turku.

Statistical analysis

Differences between groups in mean values of age and duration of symptoms before diagnosis was tested with use of one-way analysis of variance. The significance of association of progression of pulmonary changes in chest radiographs and general scores on HRCT, as well as clinical symptoms and progression of pulmonary abnormalities, were tested with Fisher's exact test. The *P* values less than .05 were interpreted as statistically significant. Calculations were performed with SPSS software (SPSS for Windows, release 8.01/1998, SPSS, Chicago, Ill).

RESULTS

Chest radiograph

Changes in the chest radiograph were seen in 19 of the 22 (86%) patients (Table II). Parenchymal interstitial fibrosis was the most common finding and it was seen in all patients with pulmonary changes. Bronchiectasis was seen in 3 (14%) and pleural thickening in 5 (23%) patients. Abnormalities were classified as advanced in 5 patients.

The right middle lobe and the left upper and the left lower lobes were the most common sites of abnormal changes.

HRCT

All but 1 of the 22 (95%) patients showed abnormalities in the HRCT study (Table II). There was no significant correlation between the duration of symptoms before diagnosis or the age at the time of diagnosis with the presence of HRCT findings (data not shown). Fibrosis was found in 18 (81%) patients. It was commonly found in the lower lobes and in the left upper lobe. Advanced pulmonary fibrosis was seen in 3 patients, of whom 1 showed honeycombing. Bronchiectasis was seen in 16 (73%) patients and it was graded as moderate or advanced in 13 patients. Bronchiectatic changes were dispersed and they were also seen in the upper lobes. However, the right middle lobe and the lower lobes were most frequently affected (67%). Parenchymal scarring was seen in 10 patients. Other findings such as ground-glass opacity (4 patients), pleural thickening (8 patients), emphysema (1 patient), bulla (1 patient), atelectasis (1 patient), or parenchymal noduli (2 patients) were either minute or rare. Abnormalities were distributed equally within the lungs. However, the right upper lobe was slightly less affected.

Three-year follow-up was carried out in 14 patients. Chest radiographs showed progression of abnormalities in 4 (29%) patients, whereas the changes had remained stable in 6 and diminished in 4 patients during the 3-year period. The progression of pulmonary changes in chest

TABLE II. HRCT and chest radiograph scoring in patients with primary hypogammaglobulinemia

Patient No./sex (y of birth)	Chest radiograph general score		HRCT general score		HRCT bronchiectasis		HRCT fibrosis-like changes	
	1994	1997	1994	1997	1994	1997	1994	1997
1/M (-29)	0	0	2	3	2	3	0	1
2/F (-59)	2	3	2	3	2	3	2	3
3/M (-59)	1	1	2	3	0	0	0	2
4/F (-44)	3	NA	3	NA	0	NA	2	NA
5/M (-81)	1	0	0	0	0	0	0	0
6/F (-35)	2	NA	2	NA	0	NA	2	NA
7/F (-43)	1	1	1	1	0	0	0	1
8/F (-86)	0	2	1	2	0*	1	0	2
9/M (-54)	1	0	2	2	1	0	2	2
10/M (-39)	2	3	3	3	1	2	3	3
11/F (-25)	1	0	2	1	1	1	1	1
12/F (-57)	3	3	3	3	3	2	3	3
13/M (-67)	0	0	0	1	0	0	0	1
14/F (-61)	NA	3	NA	3	NA	1	NA	3
15/F (-54)	NA	0	NA	2	NA	2	NA	1
16/F (-40)	NA	3	NA	3	NA	2	NA	1
17/M (-48)	NA	2	NA	2	NA	2	NA	2
18/M (-60)	NA	2	NA	3	NA	3	NA	2
19/M (-87)	3	1	3	3	3	3	1	2
20/M (-62)	1	NA	3	NA	3	NA	3	NA
21/M (-64)	1	2	2	2	0	1	2	2
22/M (-73)	0	0	3	3	2	2	0	1

M, Male; F, female; 0, no changes; 1, mild changes; 2, moderate changes; 3, advanced changes; NA, data not available.

TABLE III. PFT results in patients with primary hypogammaglobulinemia

Patient No./ sex (y of birth)	FEV ₁ (% of predicted)	FEV ₁ /FVC (% of predicted)	MEF ₅₀ (% of predicted)	Diffusion capacity (% of predicted)
1/M (-29)	69	89	48	67
2/F (-59)	104	98	110	72
3/M (-59)	79	94	72	55
6/F (-35)	91	108	78	49
7/F (-43)	105	90	82	104
9/M (-54)	67	69	36	93
10/M (-39)	74	78	43	108
11/F (-25)	89	86	46	106
12/F (-57)	102	99	108	91
13/M (-67)	105	99	123	116
14/F (-61)	109	99	109	122
15/F (-54)	100	103	106	102
18/M (-60)	125	100	111	114
21/M (-64)	100	103	103	86
22/M (-73)	139	126	144	120

Values are from first pulmonary testing. Patient numbers refer to numbers in Tables I and II. M, Male; F, female; diffusion capacity. DL_{CO} SB, Single-breath diffusing capacity for carbon monoxide (mmol/min/kPA).

radiographs was not significantly associated with progression of general scores on HRCT (data not shown). General scores on HRCT increased in 5 (35%) of the 14 patients, decreased in 1, and remained the same in 8 patients (Table II). However, progression had occurred in

a specific HRCT finding in 8 (59%) of the 14 patients. Bronchiectasis showed progression in 5 patients. In 3 patients bronchiectasis was less severe than at the previous examination. Fibrosis-like changes showed progression in 8 patients. In 6 patients the HRCT findings were unchanged. The duration of symptoms before diagnosis did not correlate significantly with the progression on HRCT findings (data not shown).

All 14 patients completed the questionnaires. The mean number of infections during the 3 years was bronchitis 1.21 (range 0-5), pneumonia 0.45 (range 0-3), sinusitis 0.93 (range 0-5), and otitis media 0.86 (range 0-10). The patients had had a mean of 2.21 antibiotic treatments (range 0-9) during the 3 years. The total number of antibiotic treatments given to patients had diminished from 38 per year (the year before the study) to 24 per year (the last year of the study) after the increase in the IVIG dosage at the onset of the study in patients with serum IgG concentrations below 5 g/L (Table I). Three (21%) of the 14 patients had deterioration in their exertion capacity during the 3 years. Sputum production in the mornings was moderate or rich in 10 patients and mild in 3 patients; all those patients had bronchiectasis. Sputum production was not associated with the worsening of pulmonary abnormalities ($P = 1.00$).

PFT

The measurements showed obstruction in 5 (33%) of the 15 patients (Table III). Obstruction was considered

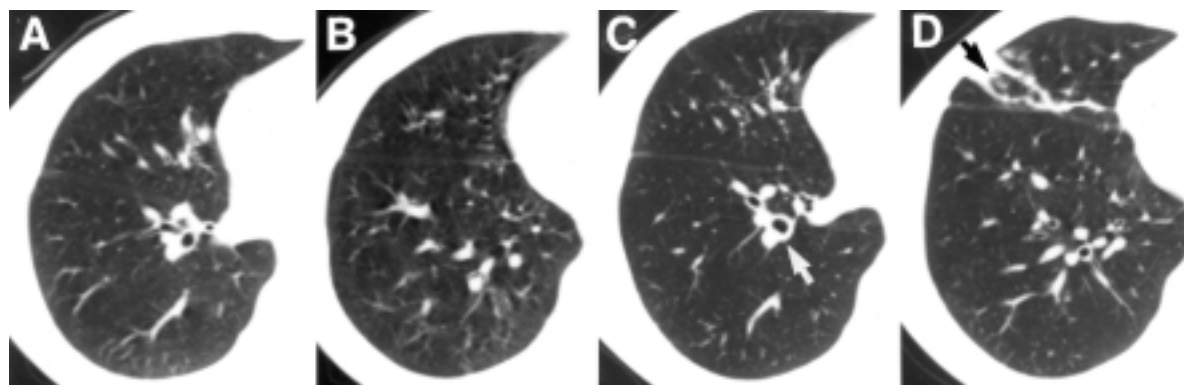


FIG 1. Two consecutive HRCT images of right lung of girl with CVID at age 8 years (**A, B**) and at age 11 years (**C, D**). Despite breathing artifacts, peribronchial thickening (*white arrow*) and progressive scarring changes (*black arrow*) can be seen in right middle lobe. However, there was no evidence of clinical pulmonary infections during 3 years. Patient was receiving adequate immunoglobulin replacement therapy, with serum IgG concentrations higher than 5 g/L. Chest radiography did not show any changes.

moderate in 3 patients (patients 1, 9, and 10). It was located in both small and large airways in 4 patients and only in large airways in 1 patient. Two patients had a mild and 2 had a moderate decrease in diffusion capacity (Table III). PFT showed deterioration after 2 years in 4 of the 10 re-examined patients, but in another 4 patients the PFT values had improved (data not shown).

DISCUSSION

Early diagnosis of primary hypogammaglobulinemia is considered to be of importance because intensive treatment may prevent the development and progression of pulmonary changes.^{1,4-8} However, diagnosis of hypogammaglobulinemia is often delayed. In this study one third of the patients had recurrent respiratory infections for more than 5 years before the diagnosis of hypogammaglobulinemia. Pulmonary abnormalities had already developed in all but 1 of the 22 patients by the time of the first HRCT imaging. Seventeen patients had a history of pneumonia, but moderate bronchiectasis was also found in 1 patient with no history of pneumonia or recurrent bronchitis. As shown in previous studies,^{7,16} HRCT was a sensitive imaging method in revealing pulmonary changes. It showed bronchiectasis in 16 patients, whereas chest radiography showed bronchiectasis in only 3. HRCT also showed fibrosis-like changes in patients whose chest radiographs were regarded as normal. Fibrosis-like changes were the most common abnormalities in our patients. Fibrosis is generally considered a nonspecific end-result triggered by diverse factors (eg, by an inflammatory process). Injury to the epithelium and basement membranes is necessary for the fibrotic process to occur.¹⁷⁻¹⁹ Bronchiectasis was another major finding and it also confirms the chronic lung damage because it is considered an irreversible dilatation of the bronchus.²⁰ Bronchiectasis was most commonly widespread or predominant in the lower lobes. This finding is consistent with the previous reports.^{6,7}

The 3-year follow-up revealed progression of pul-

monary changes in half the patients. It is important to emphasize that silent progression of pulmonary abnormalities developed in 5 patients. Two of these patients were children, an 8-year-old girl with CVID (patient 8) and a 7-year-old boy with XLA (patient 22). The chest radiograph and HRCT of the girl were normal at the initial visit. She had had 2 lobar pneumonias before hypogammaglobulinemia was diagnosed but no lower respiratory tract infections after the diagnosis of hypogammaglobulinemia. Her serum IgG concentrations had remained more than 5 g/L while receiving IVIG during the follow-up. The follow-up HRCT revealed parenchymal scarring in the right middle lobe (Fig 1) and bronchiectasis in both lower lobes. The boy already had advanced bronchiectasis at the initial visit. He had had no pneumonia during the 3-year follow-up. His chest radiograph changes had diminished, but fibrotic changes in HRCT had increased.

Our follow-up findings differ from those of the 2 earlier follow-up studies of pulmonary disease in hypogammaglobulinemia.^{5,21} In these studies only chest radiographs and PFT, but not HRCT, were used to evaluate the pulmonary disease. Deterioration of pulmonary status did not occur in patients receiving immunoglobulin replacement therapy and prophylactic antibiotics. Prophylactic antibiotics were not used in our patients. It has to be stressed that there are no prospective placebo-controlled studies of the beneficial effect of prophylactic antibiotics in patients with hypogammaglobulinemia, although they are commonly used.²¹ In 1 study of immunocompetent patients with bronchiectasis²² long-term antibiotic therapy had no effect on the sputum inflammatory activity (eg, neutrophil chemotactic activity and elastolytic activity) once the acute lower respiratory tract infection had resolved.

The results of the pulmonary function tests were not consistent with the radiologic findings. This is in keeping with previous reports.^{4,7} One patient (patient 12) had normal PFT values and yet had advanced pulmonary abnormalities, including honeycombing. In contrast,

another patient (patient 9) had a normal chest radiograph and HRCT showed moderate fibrotic changes but no bronchiectasis. Nonetheless, he had decreased PFT values, which had deteriorated during 2 years. Chronic sputum production was the only subjective symptom of pulmonary abnormalities in our patients. None of the patients had hemoptysis, which was the only clinical symptom suggested to correlate with the structural abnormality in the study of Obregon et al.⁷

Our study showed that progression of bronchiectasis occurred despite adequate immunoglobulin replacement therapy. The attainment of through serum IgG concentrations of more than 5 g/L in the treatment of patients with hypogammaglobulinemia is shown to provide better protection against infections than lower IgG concentrations.^{3,8} In our study the immunoglobulin dosage was increased in 11 of the 22 patients after the recognition of pulmonary changes by HRCT. After the IVIG dosage was increased, the number of antibiotic treatments decreased in a year by 37%. However, worsening of pulmonary abnormalities occurred in 8 patients during the follow-up, although 7 of them had achieved the recommended (>5 g/L) serum IgG concentration. It should be studied further whether the normal serum IgG concentrations (6.8-15.0 g/L) would prevent development of pulmonary abnormalities. There are today new approaches to the treatment of bronchiectasis, such as inhaled glucocorticosteroids²³ and nonsteroidal anti-inflammatory drugs,^{24,25} targeted at down-regulating the inflammation in the bronchi. Aerosolized antibiotics are also used to decrease sputum production and purulence in patients with bronchiectasis.²⁶

In conclusion, our study confirms that pulmonary abnormalities develop in most patients with primary hypogammaglobulinemia. A new finding is that silent progression of pulmonary changes may occur in patients despite an appropriate immunoglobulin replacement therapy. HRCT is the method of choice in depicting pulmonary changes. Therefore regular HRCT examinations are recommended to optimize pulmonary care. It remains to be clarified whether it would be possible to prevent development of pulmonary abnormalities by use of even higher doses of IVIG or by adding long-term antibiotics or anti-inflammatory drugs to the treatment of patients with primary hypogammaglobulinemia.

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