

Retrospective analysis of the incidence of pulmonary disease in hypogammaglobulinemia

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To determine the best predictors of chronic pulmonary disease in patients with hypogammaglobulinemia, we evaluated the clinical records, chest x-ray films, and pulmonary function tests of 10 patients with X-linked agammaglobulinemia (XLA) followed for a mean of 12.5 years, and 12 patients with common variable immunodeficiency (CVID) followed for a mean of 10.5 years. These patients, most of whom were treated with intramuscular gamma globulin and long-term oral antibiotics, had very few pneumonias after diagnosis. The patients with XLA had 0.10 pneumonias per treatment year, and the patients with CVID had 0.18 pneumonias per treatment year. Seven of the 10 patients with XLA had normal chest x-ray films 8 to 15 years after diagnosis, and none had bronchiectasis. Pulmonary disease was more common and more severe in the group with CVID, but five patients in this group also had normal chest x-ray films after long follow-up. In the entire group of 22 patients, nine of the 10 patients with abnormal chest x-ray films on most recent evaluation already had pulmonary disease at the initial visit ($p = 0.00002$). These studies indicate that the best predictors of good pulmonary function in patients with hypogammaglobulinemia are early diagnosis and good compliance with gamma globulin replacement therapy and oral antibiotics. (J ALLERGY CLIN IMMUNOL 1991;88:96-104.)

Key words: X-linked agammaglobulinemia, common variable immunodeficiency, gamma globulin, pneumonia, antibiotics, immunodeficiency, pulmonary function tests, atelectasis, obstructive lung disease

Chronic pulmonary disease is the most common long-term complication in patients with hypogammaglobulinemia.¹⁻⁵ Recurrent or persistent infections with *Haemophilus influenzae*, *Streptococcus pneumoniae*,^{1,3,5-7} and other infectious organisms can result in bronchiectasis, chronic atelectasis, and pulmonary fibrosis.¹⁻⁷ Patients often have a chronic cough, and dyspnea, cor pulmonale, and respiratory failure may develop.¹⁻⁴ In one series of patients, 90% of the in-

Abbreviations used

XLA:	X-linked agammaglobulinemia
PFT:	Pulmonary function test
TLC:	Total lung capacity
CVID:	Common variable immunodeficiency disease
CHOP:	Children's Hospital of Philadelphia
OAD:	Obstructive airway disease

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dividuals had experienced at least one pneumonia, and 38% of deaths were due to chronic pulmonary disease and cor pulmonale.¹

Recent advances in therapies available for patients with hypogammaglobulinemia, including new broad spectrum antibiotics and intravenous gamma globulin preparations, can be expected to decrease the incidence of chronic pulmonary disease in these patients. However, when several aspects of therapy are changed at once, it may be difficult to determine which is

responsible for the improvement. To determine which patients were more likely to develop chronic pulmonary disease and therefore benefit most by very aggressive therapy, we examined the records, including chest x-ray films and PFTs, for 22 patients with hypogammaglobulinemia who had been receiving therapy for a mean of 12 years. We found that the incidence of pulmonary disease in our patient population was lower than the incidence usually reported and that the strongest predictor of chronic pulmonary disease after many years of therapy was chronic pulmonary disease at the initial visit. This finding suggests that early diagnosis and initiation of therapy may be the most important mechanisms in reducing the incidence of chronic pulmonary disease in patients with hypogammaglobulinemia.

SUBJECTS AND METHODS

All patients with hypogammaglobulinemia observed in the immunology clinic at CHOP between 1975 and 1988 were included in this study, with the following exceptions: (1) children who were too young to reliably perform PFTs, (2) patients with incomplete records (two patients), and (3) patients with external chest deformities or who had an additional clinical diagnosis associated with parenchymal lung disease (two patients). Of the 22 patients studied, 10 had XLA and 12 had CVID. Twelve of these patients received their medical care exclusively at CHOP. All patients with XLA were male patients who had the onset of recurrent infection in the first several years of life. These patients had markedly decreased numbers of B cells in the peripheral circulation. Nine of the 10 had a previously affected family member, and the remaining patient's mother was identified as a carrier of XLA on the basis of nonrandom X chromosome inactivation in B cells.⁸ The group with CVID was quite heterogeneous, six male and six female patients. Patients, 15, 18, and 20 had autoimmune disease as well as hypogammaglobulinemia⁶; patient 14 had a chromosomal breakage syndrome,⁹ and patient 17 was a female patient whose disease was phenotypically identical to XLA.

Patients were treated with intramuscular gamma globulin (100 mg/kg/21 days) unless they had an acute infection, an infection resistant to therapy, or inadequate muscle mass. Intravenous gamma globulin (200 to 300 mg/kg/28 days) was administered to patients 6, 12, and 15. The gamma globulin was frequently administered by a local physician. Patients 11, 15, 18, and 19 were treated with fresh-frozen plasma before intravenous gamma globulin was available. Most patients, particularly patients younger than 15 years of age, were treated with daily antibiotics (amoxicillin or trimethoprim sulfamethoxazole). Patients receiving both gamma globulin replacement and antibiotics on a regular basis were considered to be receiving optimal treatment.

Sequential chest radiographs from each patient were evaluated by a radiologist who was unaware of the patient's clinical status at the time of the examination. The films were

also retrospectively analyzed by the authors whose interpretations were concordant with interpretations of the radiologist. All PFTs performed at CHOP were evaluated for each patient. Eighteen of the 22 patients had two or more PFTs for evaluation. PFT data that had been obtained during an episode of acute pulmonary infection were excluded. Flow-volume curves were obtained with a Hewlett-Packard 47804 computerized pulmonary function testing system (Hewlett-Packard Co., Waltham, Mass.). Flow rates were measured with a hand-held pneumotachograph (Hewlett-Packard 47304A), and the signal was digitalized and integrated for volume. Functional residual capacity was measured in a constant-volume whole-body plethysmograph (Warren E. Collins, Inc., Braintree, Mass.) according to the method of Dubois et al.¹⁰ Vital capacity was determined by spirometry with the pneumotachograph. Residual volume was calculated from the functional residual capacity and spirometric data. Published regression formulas were used to derive the FVC, FEV₁, mean forced expiratory flow between 25% and 75% of the FVC, and the TLC.¹¹ OAD was diagnosed if the FEV₁/FVC was <95% confidence interval.¹¹ Mild obstruction was present if the FEV₁/FVC was <80% of predicted. Moderate obstruction was present if the ratio was <70% of predicted. Severe obstruction was present if the ratio was <60% of predicted. Restrictive lung disease was present if the TLC was <95% confidence interval.¹² Restriction was classified as mild if the TLC was <80% of predicted, classified as moderate if TLC was <70% of predicted, and classified as severe if TLC was <60% predicted.

Statistical analyses were performed with the Student's *t* test and Fisher's exact test.

RESULTS

Patients' characteristics

The 22 patients in this study could be divided into two diagnostic categories, XLA and CVID (Tables I and II). Compared to the patients with CVID, patients with XLA were younger at the onset of symptoms and had a shorter duration between the onset of symptoms and diagnosis. At the time of this study, the patients with XLA were younger than patients with CVID but had been receiving therapy for hypogammaglobulinemia for a longer period of time. The 10 patients with XLA had been receiving therapy for a mean of 12.5 ± 3.6 years, providing 125 treatment years for study. The number of treatment years was calculated from the initiation of gamma globulin therapy to the time of the most recent evaluation of the patient or the completion of the study in 1988. The 12 patients with CVID had been receiving therapy for a mean of 10.5 ± 5.6 years, providing 126 treatment years. Seven of the 10 patients with XLA and five of the 12 patients with CVID were initially diagnosed at CHOP and received all of their subspecialty care at that institution.

TABLE I. Patient's characteristics

Patient No.	Age of diagnosis	Years between onset of symptoms and diagnosis	No. of pneumonias		All care at CHOP	Treatment years
			Before diagnosis	After diagnosis		
XLA				5	—	21.1
1	3.5	1.0	0	1	+	12.9
2	0.8	—	0	2	—	11.0
3	0.8	—	0	0	+	9.0
4	2.5	0.1	0	1	+	8.5
5	0.8	—	0	1	—	15.5
6	8.5	3.5	3	0	+	10.7
7	0.2	—	0	1	+	12.1
8	2.7	0.1	1	1	+	12.0
9	7.0	5.5	1	1	+	12.1
10	5.5	3.7	1	2	—	15.5
CVID						
11	10.5	0.1	>1	1	—	11.4
12	26.0	1.0	0	0	+	4.7
13	21.0	4.5	3	1	—	18.5
				3	—	18.7
14	6.0	2.0	0	8	+	12.5
15	3.3	2.1	2			
16	6.0	5.0	5	0	+	12.5
17	2.0	1.2	2	3	—	9.8
				5	—	9.8
18	12.0	11.2	0	0	—	0.3
19	15.0	10.0	>3	0	+	5.0
20	18.4	10.4	>3	0	+	6.9
21	28.5	0.2	1			
22	1.5	1.3	0			

CXR, Chest x-ray; IM, intramuscular; IV, intravenous; FFP, fresh-frozen plasma.

TABLE II. Comparison of patient data for XLA and CVID

	XLA	CVID	<i>P</i> Value
No. of patients	10	12	
Mean age at diagnosis	3.2 ± 2.9	12.5 ± 9.3	<0.01
Mean age at onset of symptoms	1.8 ± 1.4	8.5 ± 9.8	<0.05
Mean duration between onset of symptoms and diagnosis	1.4 ± 2.0	4.1 ± 4.2	0.08
Mean current age	16.3 ± 5.3	23.5 ± 7.9	<0.05
Mean years receiving treatment	12.5 ± 3.6	10.5 ± 5.6	0.34
No. of treatment years	125	126	

At diagnosis, the mean immunoglobulin concentrations were comparable for the two groups. The IgG and IgM were 192.7 ± 164 mg/dl and 29.2 ± 44.8 mg/dl, respectively, for patients with XLA, and 174.6 ± 160 mg/dl and 27.0 ± 24.6 mg/dl for the patients with CVID. The average IgA concentrations

were 3.7 ± 5.1 mg/dl for the group with XLA and 12.0 ± 21.3 mg/dl for the group with CVID. During gamma globulin replacement, trough IgG levels for the two groups of patients did not differ significantly, 256 ± 70 mg/dl for patients with XLA versus 298 ± 175 mg/dl for patients with CVID.

Replacement therapy	CXR	PFT
IM	Atelectasis	Mild obstruction
IM	Atelectasis	Mild obstruction
IM	Atelectasis	Mild obstruction
IM	Normal	Mild obstruction
IM	Normal	Normal
IM/IV	Normal	Normal
IM	Normal	Normal
IM	Normal	Normal
IM	Normal	Normal
IM	Normal	Normal
FFP/IM	Bronchiectasis Atelectasis	Moderate obstruction
IM/IV	Bronchiectasis Diffuse interstitial changes	Mild obstruction
IM	Bronchiectasis	Mild obstruction
	Bronchiectasis	Severe obstruction
IM	Normal	Mild obstruction
FFP/IV	Bronchiectasis	Mild obstruction
IM	Diffuse interstitial changes	
IM	Normal	Mild obstruction
	Atelectasis	Mild restriction
FFP	Interstitial markings	
FFP/IM	Bronchiectasis	Mild restriction
IM	Normal	Normal
IM	Normal	Normal
IM	Normal	Normal

Pneumonias

After diagnosis, 13 episodes of radiographically documented pneumonia occurred in eight patients with XLA. There were two individuals in the group with XLA who never developed pneumonia. This represents 0.10 episodes of pneumonia per treatment year. Hospitalization for intravenous antibiotics was necessary for seven of the 13 pulmonary infections. Bacterial etiologies based on sputum cultures included *H. influenzae* (three times) and *S. pneumoniae* (two times). For eight of the 13 pneumonias, the infecting agent was not identified.

After initiation of gamma globulin therapy, 23 episodes of pneumonia occurred in seven of the 12 patients with CVID. Five of the patients with CVID did not have any episodes of pneumonia after diagnosis. The 23 pneumonias represent 0.18 episodes of pneumonia per treatment year, nearly twice as many as observed in the group with XLA ($p = 0.30$). Of the

23 pulmonary infections in patients with CVID, 14 required hospitalization. On 12 occasions the infecting organism was identified; seven were attributed to *H. influenzae*, two to *Pneumocystis carinii*, one each to *Pseudomonas aeruginosa*, *S. pneumoniae*, and *Mycoplasma hominis*. No patients in either group experienced a necrotizing pneumonia.

Radiographic studies

Chest radiographs were performed at diagnosis and then yearly, or more often if clinical symptoms warranted. Of the seven patients diagnosed as having XLA at CHOP, one had peribronchial thickening at the initial evaluation; the other six patients had normal chest films. Two of the three patients first observed several years after diagnosis and initiation of therapy had chronic segmental atelectasis on their first evaluation at CHOP.

On the most recent chest x-ray films, all three patients who had abnormal chest x-ray results on their initial evaluation had chronic segmental atelectasis. The child who had peribronchial thickening at diagnosis at 9 months of age was noted to have developed atelectasis at 2 years of age without having had a previously documented pneumonia. The remaining seven patients who had normal chest films at the initial visit, all had normal chest films 8 to 15 years after diagnosis.

Of the five patients with CVID who were diagnosed at CHOP and received all of their subspecialty care at that institution, two patients had evidence of bronchiectasis on their first evaluation. One of these patients (no. 13) had three episodes of pneumonia in the 4½ years before diagnosis, and the other patient (no. 16) had five episodes of pneumonia in the 5 years before diagnosis. The remaining three patients had normal chest films at diagnosis and continued to have normal chest films 5 to 12 years after diagnosis. One of these three patients (no. 22) had not had any pneumonias before diagnosis, patient 21 had one pneumonia 2 months before diagnosis, and patient 17 had two pneumonias in the year before diagnosis.

Of the seven patients who were first evaluated more than a year after diagnosis, four had abnormal chest x-ray films at their initial visit. The patient with the most severe pulmonary disease (patient 14) had not had any documented episodes of pneumonia when she was diagnosed at another hospital as having hypogammaglobulinemia at 6 years of age. She was then lost to follow-up for 10 years, during which time she received regular intramuscular gamma globulin and intermittent oral antibiotics and had no infections requiring hospitalization. At her initial visit at 18 years of age, she had severe bronchiectasis. Patient 19 had

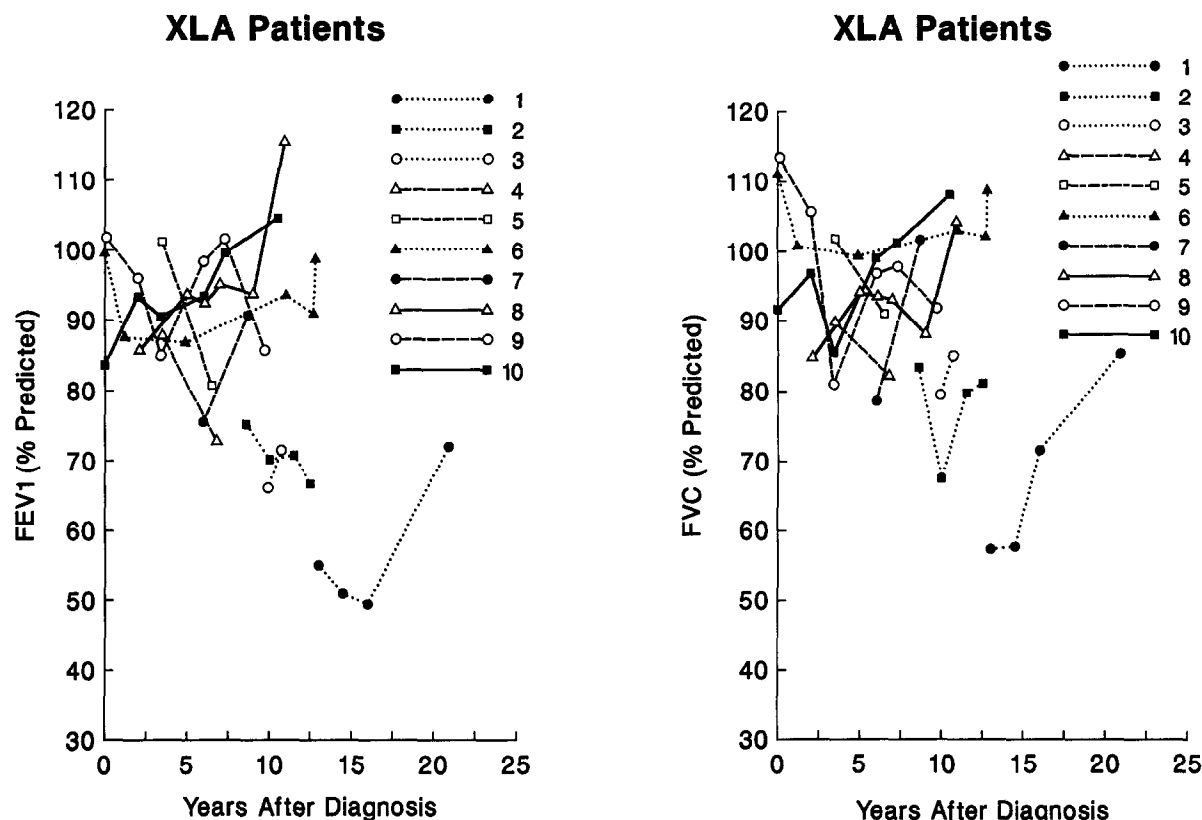


FIG. 1. Each line represents the sequential percent predicted FEV₁ (left) and FVC (right) for an individual patient with XLA. A value of $\geq 80\%$ of predicted is considered normal.

three pneumonias before diagnosis and one pneumonia between initiation of therapy and his first visit to CHOP, at which time his chest x-ray film demonstrated bronchiectasis. The number of pneumonias experienced by patient 11 before diagnosis could not be determined from medical records. When he was first evaluated at CHOP 6½ years after diagnosis, he had had one episode of pneumonia in the intervening years, and his chest x-ray film demonstrated peribronchial thickening with hyperinflation. Patient 12 had only a single pneumonia before his first visit to CHOP, at which time he was found to have peribronchial thickening and an increased reticular pattern.

On the most recent chest x-ray film, seven of the 12 patients with CVID had abnormal findings. Six of these seven patients had abnormal findings at the time of the initial visit. Five of the 12 patients with CVID had normal chest x-ray films on their most recent evaluation. This group of five patients included one who had never had a pneumonia, three who did not have any episodes of pneumonia after diagnosis, and a final patient who had two episodes of pneumonia before she started receiving therapy and had three pneumonias in 18.7 treatment years.

PFTs

Abnormal or deteriorating PFTs were observed in all the patients with abnormal chest x-ray films but were also occasionally observed in patients with normal chest x-ray films and in patients without a history of an acute infection. Changes indicative of obstructive lung disease were the most common abnormalities in both patient groups.

Because patients with XLA were diagnosed at a younger age, most patients were unable to perform PFTs until several years after diagnosis. However, at their initial evaluation, seven of 10 patients with XLA had normal PFTs. Three of the patients had evidence of mild obstructive disease; these were the three patients with segmental atelectasis as revealed on chest x-ray film. On their most recent PFTs, these three patients continued to demonstrate decreased FEV₁ and forced expiratory flow between 25% and 75% of the FVC, although their PFTs were unchanged or improved compared to their initial evaluation (Fig. 1). One patient with XLA (patient 4) who had never had a pneumonia and who had normal chest x-ray films also had mild obstructive disease, as assessed by PFTs. The current ages of the patients with XLA with

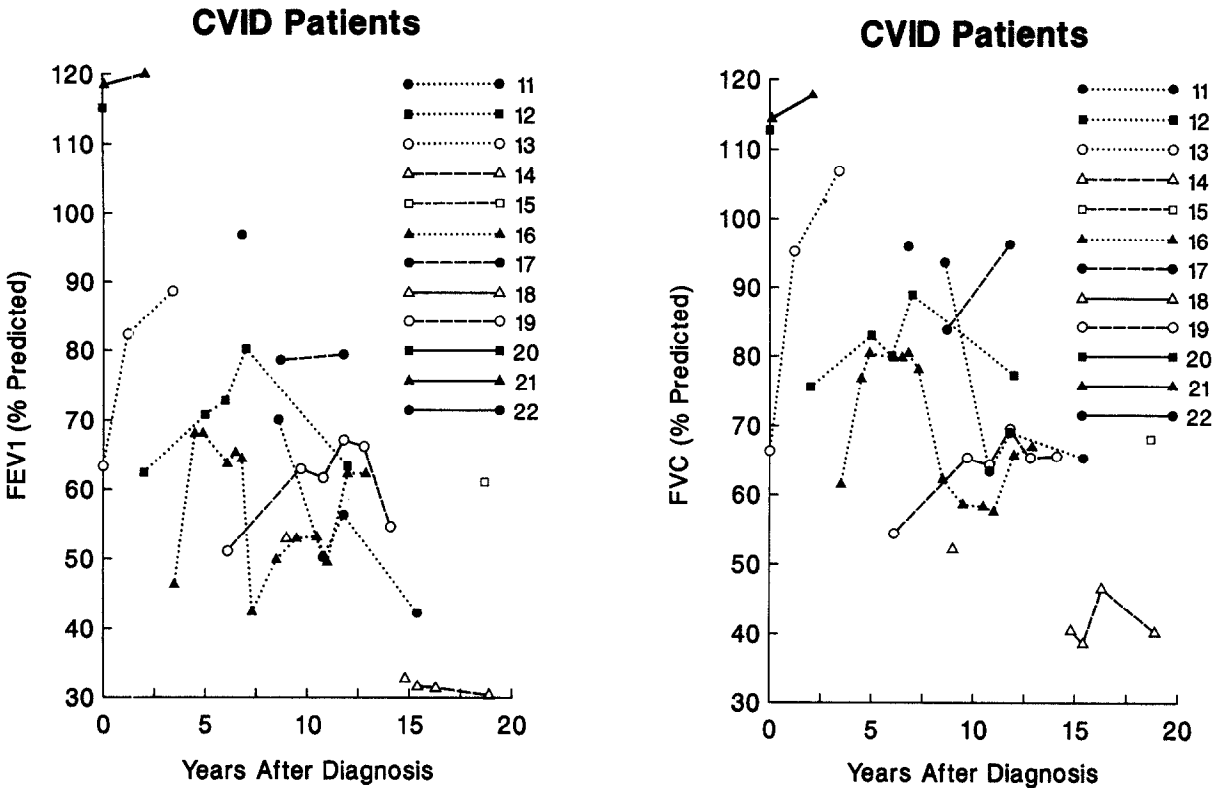


FIG. 2. Each line represents the sequential percent predicted FEV₁ (left) and FVC (right) for an individual patient with CVID.

TABLE III. Characteristics in patients with CVID based on lung disease

	Restrictive	Obstructive	Normal
No. of patients	2	7	3
No. of pneumonias after diagnosis	8	15	0
No. of pneumonias per treatment years	0.41	0.16	0
Current age (yr)	23.3 ± 2.1	24.4 ± 7.9	21.6 ± 12.4
Duration between onset of symptoms and diagnosis	10.6 ± 0.85	2.3 ± 1.8	4.0 ± 5.6
Means years receiving treatment	9.8 ± 0	13.4 ± 4.8	4.1 ± 3.4

normal PFTs (15.9 ± 5.4 years) and patients with abnormal PFTs (16.9 ± 5.8 years) were not significantly different ($p = 0.78$). The duration of therapy was 11.8 ± 2.3 years for the group with no PFT abnormality and 13.5 ± 5.3 years for the group with abnormal PFTs ($p = 0.5$).

Pulmonary function abnormalities were more common and more severe in the group with CVID (Fig. 2). Seven patients with this diagnosis had OAD, five had mild, one had moderate, and one had severe OAD. Reversibility of small airway disease with bronchodilators was demonstrated in two of these patients. Mild restrictive disease was found in two patients. These two patients had restrictive changes when they

were first evaluated at CHOP. There was no known predisposing cause except to note the greater frequency of pneumonia per treatment years and the longer duration between onset of symptoms to diagnosis in patients with restrictive lung disease (Table III). None of the patients developed mixed obstructive-restrictive disease. Serial PFTs were available on one patient with restriction, six patients with obstruction, and one patient with normal pulmonary function. The patient with restriction demonstrated no deterioration in TLC over time. The FEV₁ was used to assess progression over time for those patients with obstructive lung disease. Five patients demonstrated no change ($>15\%$ change in FEV₁), and one patient deteriorated.

TABLE IV. Correlation of chest x-ray findings at the initial clinic visit to findings at the completion of the study

	No. of patients with chest x-ray at initial visit	
	Normal	Abnormal
Normal chest x-ray film at completion of study	12	0
Abnormal chest x-ray film at completion of study	1	9

Patient 11 had significant deterioration on PFTs 1 month before his death. Patient 15 had no PFT abnormality on initial examination, but on follow-up, her PFT findings were consistent with criteria for mild obstructive lung disease. There was no significant difference in current age for patients with CVID with normal (21.6 ± 12.4 years) and those with abnormal (24.1 ± 8.0 years) PFTs ($p = 0.89$). When duration of treatment is compared, patients with CVID with normal PFTs were treated for 4.1 ± 3.4 years, whereas patients with abnormal PFTs were treated for 12.8 ± 4.4 years ($p = 0.02$).

Outcome

At the completion of this study, 20 of the 22 patients were living. Both deaths were in young adults with CVID; patient 11 died in 1983 of chronic active hepatitis, possibly related to long-term therapy with fresh-frozen plasma, and patient 18 died of *P. carinii* pneumonia in 1982 while she was receiving immunosuppressive therapy for autoimmune disease. Two patients with CVID have restricted activities, patient 14 because of developmental disabilities related to her chromosomal breakage syndrome, and patient 15 because of severe juvenile rheumatoid arthritis. The remaining 18 patients had normal growth and development, and at the completion of the study, they were full-time students or had full-time employment.

DISCUSSION

In a long-term follow-up study of 22 patients with hypogammaglobulinemia, who were receiving therapy before intravenous gamma globulin was available, we found a relatively low incidence of pneumonia after diagnosis. The 10 patients with XLA had a mean 0.10 pneumonias per treatment year, and the 12 patients with CVID had a mean of 0.18 pneumonias per treatment year. As presented in Table IV, most patients who had normal chest x-ray films at the initial visit continued to have normal films and normal PFTs 8 to

18 years later ($p = 0.00002$). For those patients who had abnormal chest x-ray films or PFTs at the first visit, progression of the pulmonary disease was rare.

In our group of patients, there was higher incidence of pulmonary disease in patients with CVID compared to patients with XLA. This finding cannot be attributed to differences in treatment or trough IgG concentrations. The longer duration between the onset of symptoms and diagnosis in the patients with CVID (4.1 ± 4.2 years compared to 1.4 ± 2.0 years in patients with XLA) may in part explain the difference. Those patients who had had several pneumonias before diagnosis and who had developed bronchiectasis were more likely to experience pneumonias after diagnosis. However, the higher incidence of pulmonary disease in patients with CVID may also be due to intrinsic differences between CVID and XLA. T cell defects that occur in patients with CVID but not in patients with XLA, may predispose patients with CVID to a wider spectrum of infectious diseases. In addition, autoimmune disorders are common in patients with CVID, and there may be an autoimmune component to the pulmonary disease in some of the patients with CVID.

The incidence of pulmonary disease both in patients with XLA and CVID reported in this study is less than that usually described in the literature. In a survey study that included 96 patients with XLA, Lederman and Winkelstein¹ reported that 41% of patients older than 10 years of age had chronic pulmonary disease. Nine of these patients developed cor pulmonale, and six of nine patients died of their pulmonary disease. In a study of 30 children with CVID, Hausser et al.³ noted that 26 had five or more radiologically proven pneumonias, and 16 patients had bronchiectasis. Watts et al.² studied 32 patients with CVID, including both children and adults. Twenty-eight of these 32 patients had three or more pneumonias and 14 had bronchiectasis. Dukes et al.⁴ compared the number of pneumonias per year before and after the initiation of intramuscular gamma globulin and intermittent antibiotics in a group of 55 adults with CVID. Two or more pneumonias per year were observed in 69% of the patients before therapy and 22% of the patients after therapy was started. There was a mean of approximately 11 years between the onset of symptoms and diagnosis in this group of patients, and 87% had abnormal chest x-ray films.

Until recently, intramuscular gamma globulin was the accepted method of immunoglobulin replacement for patients with hypogammaglobulinemia. However, there are now several preparations of intravenous gamma globulin available that can be used to provide patients with normal concentrations of serum IgG.

This finding has prompted some investigators to advocate this method of therapy for all patients with hypogammaglobulinemia.^{7, 13-17} In a 2-year crossover study, Ammann et al.¹⁸ evaluated 34 patients with hypogammaglobulinemia and concluded that the efficacy of intravenous and intramuscular gamma globulin at 100 mg/kg/mo were comparable since no episodes of pneumonia were observed in either group. Cunningham-Rundles et al.¹⁷ evaluated 21 patients with hypogammaglobulinemia while they were receiving gamma globulin, 40 to 60 mg/kg intramuscularly or 300 mg/kg intravenously, every 3 weeks for 1 year. The patients receiving intramuscular replacement experienced six episodes of pneumonia (0.286 episodes per treatment year), whereas patients receiving intravenous replacement had three episodes (0.143 episodes per treatment year). Roifman et al.¹⁹ evaluated a selected group of seven patients with hypogammaglobulinemia who were experiencing one or more acute infections per month. Patients who had been receiving intramuscular gamma globulin were changed to high-dose (600 mg/kg/mo) intravenous replacement. Twelve episodes of pneumonia occurred while intramuscular gamma globulin was administered, but no episodes occurred during intravenous replacement.

Of the patients included in our study, only three were treated with intravenous gamma globulin, one, for chronic pulmonary disease (patient 12), another patient, for persistent neck abscesses (patient 6), and the third patient, for inadequate muscle mass (patient 15). The remaining patients were treated with intramuscular gamma globulin, and most patients received daily oral antibiotics. The frequency of pneumonia in these patients was equal to or less than that reported for most patients receiving intravenous gamma globulin. The low frequency of pneumonias in this group of patients might be explained by several factors. First, it may be that the proportion of patients with normal pulmonary function at the time of diagnosis was unusually high in our patient population. Second, our aggressive use of oral antibiotics may have reduced the incidence of infection. Finally, compliance with intramuscular gamma globulin may have been better than at most centers. Although compliance was difficult to document, it was our clinical impression that pneumonias occurred more frequently when the patients were receiving inadequate doses of either gamma globulin or antibiotics.

Other investigators have demonstrated that patients with hypogammaglobulinemia and significant pulmonary disease benefit from doses of gamma globulin that can be achieved only with intravenous therapy. However, this method of therapy continues to be very

expensive and time consuming. Our data indicate that patients with normal lung function at diagnosis can be maintained on intramuscular gamma globulin and long-term antibiotics without the development of progressive pulmonary disease. Because the lung disease in patients with hypogammaglobulinemia may be insidious in onset and progression, we recommend annual chest x-rays and PFTs. These studies should help the physician prescribe the appropriate therapy for each individual patient with hypogammaglobulinemia.

Delay in diagnosis and initiation of therapy for patients with hypogammaglobulinemia may predispose these patients to chronic lung disease. Physicians should consider evaluating the immune function of any individual who has two or more bacterial pneumonias in a 10-year period. The lung disease of patients with hypogammaglobulinemia need not be progressive, provided there is good compliance and an aggressive treatment regimen that includes the liberal use of antibiotics and regular gamma globulin replacement.

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The effect of cetirizine on the human isolated bronchus: Interaction with salbutamol

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The effects of cetirizine (C), a new generation, nonsedative, H₁-antihistamine drug, were studied on human isolated bronchi. C is a potent antagonist of the bronchial muscle contraction induced by histamine, irrespective of whether C is administered by cumulative addition or prophylactically. In the former case, this effect of C was significant at a concentration of 3×10^{-8} mol/L and was maximal at a concentration of 10^{-5} mol/L. The $-\log$ of concentration of C causing 50% of the maximal effect induced was 7.30 ± 0.05 ($n = 6$), and the effect produced was not significantly modified by bronchial epithelium removal. When C was administered prophylactically, the concentration-response curves to histamine were displaced to the right, but the reduction of maximum histamine response suggests a noncompetitive type of antagonism. C is devoid of notable anticholinergic effects. At concentrations of 10^{-8} to 10^{-7} mol/L, C proved capable of enhancing the relaxant effect produced by salbutamol (10^{-7} to 3×10^{-7} mol/L) on human isolated bronchi that had been contracted by either histamine or acetylcholine (ACh). The synergy appeared to be additive or potentiating, depending on salbutamol (SAL) concentrations. Under similar conditions, mepyramine does not potentiate the effects of SAL against histamine. Finally, at concentrations of 10^{-8} to 10^{-6} mol/L, C reduced the functional antagonism observed between SAL and ACh, as can be observed by the increase, in the presence of C, of the maximal relaxant effect of SAL on contractions produced by 10^{-3} mol/L of ACh. We may, therefore, conclude that C appears to be a specific antihistamine on human isolated bronchi and that it appears to potentiate the bronchodilator effect of SAL on this preparation. (J ALLERGY CLIN IMMUNOL 1991;88:104-13.)

Key words: Histamine antagonists, adrenergic β -receptor agonists, cetirizine, salbutamol, mepyramine, acetylcholine, human isolated bronchi, human airways

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