Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Comparison of pulmonary diseases in common variable immunodeficiency and X-linked agammaglobulinaemia

ASGHAR AGHAMOHAMMADI,[1,2] ABDOLREZA ALLAHVERDI,[1] HASSAN ABOLHASSANI,[2] KASRA MOAZZAMI,[2] HOOMAN ALIZADEH,[1] MOHAMMAD GHARAGOZLOU,[1] NAJMODDIN KALANTARI,[1] VAHID SAJEDI,[1] ALIREZA SHAFIEI,[1] NIMA PARVANEH,[1,2] MASOUD MOHAMMADPOUR,[1] NASSER KARIMI,[2] MOHAMMAD SALEHI SADAGHIANI[2] AND NIMA REZAEI[1,2]

[1]*Department of Pediatrics, Pediatrics Center of Excellence, Children's Medical Center, and* [2]*Growth and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran*

ABSTRACT

Background and objective: **Pulmonary disease is the most common complication in patients with common variable immunodeficiency (CVID) or X-linked agammaglobulinaemia (XLA). Pulmonary disease may progress despite immunoglobulin replacement therapy. In this study pulmonary complications were compared in patients with CVID or XLA.**

Methods: **Pulmonary complications were evaluated in 115 patients (76 with CVID and 39 with XLA) by reviewing hospital records of chest infections, pulmonary function tests and high-resolution CT scans.**

Results: **Thirty-two patients with XLA (82%) presented with 59 episodes of pneumonia before diagnosis, whereas 15 patients (38.4%) experienced pneumonia after immunoglobulin replacement therapy (1.67 vs 0.45 episodes per patient per year). Among the CVID patients, 196 episodes of pneumonia were documented in 59 patients (77.6%) before diagnosis, while 36 patients (47.3%) experienced pneumonia after therapy (1.11 vs 0.58 episodes of pneumonia per patient per year). Forty-seven (41%) patients (38 with CVID and 9 with XLA) developed chronic lung disease. The CVID patients developed more complications, including bronchiectasis and lymphoid interstitial pneumonitis, than the XLA patients.**

Conclusions: **Patients with CVID had a greater likelihood of developing lung disease, possibly due to delayed diagnosis and immune dysregulation, as compared with XLA patients. Early diagnosis of patients with primary antibody deficiencies and adequate i.v. immunoglobulin replacement therapy substantially reduces the number of pulmonary infections. However, CVID patients are prone to progression of lung disease despite optimal immunoglobulin therapy because of the nature of the disease. This important issue should be addressed in further studies.**

SUMMARY AT A GLANCE

Patients with CVID are at greater risk of developing lung complications than patients with XLA because of delayed diagnosis and possible immune dysregulation. Early diagnosis and appropriate treatment reduces the incidence of pulmonary infections in both groups of patients. However, CVID patients are prone to progressive lung disease despite optimal immunoglobulin therapy.

Key words: common variable immunodeficiency, lung complication, pneumonia, pulmonary function test, X-linked agammaglobulinaemia.

INTRODUCTION

Common variable immunodeficiency (CVID) is the most frequently occurring symptomatic primary immunodeficiency. It is a clinically heterogeneous disorder with recurrent bacterial infections, autoimmune manifestations and lymphoproliferation.[1–4] The diagnostic criteria for CVID include decreased serum immunoglobulin levels and exclusion of other well-defined primary antibody deficiencies (PAD).[5] Although various abnormalities in both the innate and adaptive immune systems have been described,[6–13] the molecular basis of CVID remains largely unknown.

In contrast, X-linked agammaglobulinaemia (XLA) is an inherited single gene disorder caused by mutations in the gene for Bruton tyrosine kinase (*BTK*) that result in developmental defects in B lymphocytes.[14–16] Affected individuals have low serum immunoglobulin levels and markedly reduced B cell numbers.[17,18] As a result, they have an increased susceptibility to

Correspondence: Asghar Aghamohammadi, Children's Medical Center Hospital, 62 Qarib Street, Keshavarz Boulevard., Tehran 14194, Iran. E-mail: aghamohammadi@sina.tums.ac.ir

Received 18 June 2009; invited to revise 17 July 2009, 8 September 2009; revised 11 August 2009; accepted 16 September 2009 (Associate Editor: Jerry Brown).

encapsulated bacteria and enteroviruses, as antibodies play a critical role in host defence against these microorganisms.[19–22]

Both CVID and XLA predispose affected individuals to recurrent respiratory tract infections, chronic bronchitis, bronchiectasis, as well as obstructive and restrictive lung diseases.[23–28] Bronchiectasis and bronchial wall thickening are well-recognized complications of PAD.[26–28] Delay in diagnosis or inadequate management may lead to permanent organ damage (e.g. bronchiectasis) and death.[23,24,29] Early diagnosis of patients with PAD and adequate immunoglobulin replacement therapy reduce the number of pulmonary infections and are considered the keys to survival and a better quality of life.[30–32]

Despite receiving optimal immunoglobulin therapy, some patients with PAD develop chronic lung disease. It is important that physicians treating patients with PAD perform baseline pulmonary function tests (PFT) for all patients, and also consider high-resolution CT (HRCT) of the chest in patients with chronic chest symptoms, in order to monitor parameters related to lung disease in patients receiving immunoglobulin replacement therapy.

Although several studies have reported the incidence of pulmonary complications in patients with CVID or XLA, there are only a few reports comparing the incidence of pulmonary complications between these diseases. Therefore, the purpose of this study was to compare the frequencies of pulmonary complications between patients with CVID and those with XLA.

METHODS

Patients

The Immunodeficiency Clinic at the Children's Medical Center affiliated to Tehran University of Medical Sciences is a referral centre for both paediatric and adult patients with primary immunodeficiency disease. A total of 115 patients with PAD (76 with CVID and 39 with XLA), who were diagnosed and treated at this centre between 1984 and 2009, were selected for this study. The diagnosis of CVID or XLA was made according to the criteria of the European Society for Immunodeficiencies and the Pan-American Group for Immunodeficiency.[5] Diagnosis of CVID was based on a reduction of at least two serum immunoglobulin isotypes (IgG, IgA and IgM) by two standard deviations from the normal mean values for age, in patients older than 2 years, because of the possibility of transient hypogammaglobulinaemia. Diagnosis of XLA was based on hypogammaglobulinaemia associated with very low numbers of circulating B cells (<1%) and detection of *BTK* mutations.[18] All patients received regular immunoglobulin replacement therapy with doses of 400–600 mg/kg/month, as well as prophylactic antibiotic therapy.

Demographic and clinical information

After obtaining approval from the ethics committee at our centre to use patient records while maintaining patient confidentiality, a two-page questionnaire was developed to capture all demographic information, including date of birth, age at onset of symptoms, age at diagnosis and history of respiratory infections and lung complications. All information was obtained by reviewing the patients' hospital records before and after diagnosis.

Diagnostic delay was defined as the time between onset of symptoms and the time of diagnosis. Duration of follow up was the time between diagnosis and the date of either the last visit or death. For each patient, the total number of episodes of pneumonia before and after diagnosis was recorded. The diagnosis of pneumonia was based on the Centers for Disease Control criteria,[33] including clinical, radiological and laboratory evidence of lower respiratory tract infection. Although sputum culture may have provided information on antimicrobial susceptibility, it is not useful for the diagnosis of pneumonia.

Pulmonary function tests

Pulmonary function was evaluated according to the American Thoracic Society guidelines,[34] using a computerized pneumotachograph (Jaeger, Wurzburg, Germany) in patients who were 6 years and older and cooperative, with patients tested in the seated position (within a volume displacement body plethysmograph). FVC, FEV_1, FEV_1/FVC and maximal mid-expiratory flow ($MMEF_{25–75\%}$) were recorded.

High-resolution CT

The HRCT was performed to confirm the presence of chronic lung disease in patients who had persistent symptoms for more than 4 weeks. HRCT was assessed using the modified Bhalla scoring method to evaluate the presence and severity of different parameters,[35–37] including: (i) the presence and extent of bronchiectasis; (ii) the average severity of bronchial dilatation; (iii) bronchial wall thickness; (iv) the presence or absence of mucus within the large airways, and separately, within the centrilobular bronchioles; (v) the extent of decreased attenuation of the lung parenchyma; (vi) the extent of bronchial wall collapse; and (vii) the extent of tracheal collapse. These parameters were scored separately for each lobe, as well as the lingula, and the total lung score was derived by summing the lobar grades; the final scores used in the analysis were obtained by summing the total lung scores of two observers. The highest possible score was 18. Bronchiectasis was recognized as bronchial dilatation, often with thickening of the walls. Bronchial dilatation was considered to be present when the internal diameter of the bronchus was greater than that of the adjacent pulmonary artery.

Table 1 Characteristics of the patients with primary antibody deficiency ($n = 115$)

Parameter	XLA	CVID	*P*-value*
Number	39	75	—
Gender (male/female)	39/0	43/33	—
Age at time of study, years (range)	12 (3–32)	17 (2–59)	0.18
Age at time of onset of symptoms, years (range)	1 (0.5–6)	2 (0.5–46)	<0.0001
Age at the time of diagnosis, years (range)	3.8 (1–24)	9 (2–54)	<0.0001
Duration of delay in diagnosis, years (range)	2 (0.3–10)	5 (1–32)	0.003
Duration of follow-up, years (range)	7 (1–21)	5 (1–22)	0.001

* Calculated by independent *t*-test.
CVID, common variable immunodeficiency; XLA, X-linked agammaglobulinaemia.

Statistical analysis

Clinical information, including PFT and HRCT results, were compared among the patient groups. Fisher's exact test and chi-square tests were used for 2×2 comparison of categorical variables, whereas *t*-tests and one-way analysis of variance with Bonferroni's test were used to compare numerical variables. Confounding variables, including delay in diagnosis and history of allergy, were excluded from the statistical analysis. Correlations between CT findings (airspace consolidation, ground-glass attenuation, reticulation, thickening of bronchovascular bundles, honeycombing, nodules and bronchiectasis) and PFT (%VC, FEV_1/FVC, %MMEF) were analysed by the nonparametric Spearman correlation coefficient. Statistical analyses were performed using StatView version 4.5 software (Abacus Concepts, Berkeley, CA, USA). A *P*-value < 0.05 was considered significant.

RESULTS

Characteristics of the patients

There were 115 patients, aged 2–59 years, who had been diagnosed with PAD, including 76 with CVID and 39 with XLA. There were 82 men and 33 women (Table 1). The median ages at the time of the study for patients with CVID and XLA were 17 and 12 years, respectively. The median age at the onset of symptoms was 2 years (range 0.5–46) for CVID patients, which was significantly higher than that of XLA patients (1 year, range: 0.5–6 years, $P < 0.001$). XLA patients were diagnosed at a younger age (median 4 years, range 1–24 years) than CVID patients (9 years, range 1–54 years, $P < 0.001$). The median lag times for diagnosis of CVID and XLA were 8 years (range 1–32 years) and 2.5 years (range 1 month to 15 years), respectively ($P = 0.003$). There was an inverse association between age of onset and delay in diagnosis ($r = -0.93$).

Forty-seven of 76 CVID patients (64.4%) and 27 of 39 XLA patients (69.2%) had respiratory manifestations as the initial presenting symptoms. Twenty-two CVID patients presented with other types of infections, including diarrhoea, urinary tract infections, conjunctivitis, candidiasis and septic arthritis. Allergic manifestations (four patients) and autoimmunity (three patients) were less frequent among this group of patients. Initial presenting symptoms in the 12 remaining XLA patients were gastrointestinal infections (10 patients), urinary tract infection (one patient) and meningitis (one patient). Immunological data, including serum immunoglobulin levels and lymphocyte subset counts at the time of diagnosis, are shown in Table 2.

Pulmonary infections before and after diagnosis

Pulmonary infections, particularly pneumonia, were the most frequent clinical manifestations in all patients (Table 3). Before diagnosis and initiation of immunoglobulin replacement therapy, 32 XLA patients (82%) and 59 CVID patients (77.6%) experienced at least one episode of pneumonia ($P = 0.03$). Twenty-seven of the 32 XLA patients (84.3%) and 45 of the 59 CVID patients (76.3%) had more than one episode of pneumonia. On average, the 32 XLA and 59 CVID patients who experienced episode(s) of pneumonia before starting immunoglobulin replacement therapy had 1.67 and 1.11 episodes of pneumonia per patient per year, respectively ($P = 0.008$). The characteristics of the XLA and CVID patients with a history of pneumonia and chronic lung disease are shown in Table 3. In order to adjust for the probable effect of 'delayed diagnosis' on the pneumonia incidence rate, XLA and CVID patients were stratified into those with delays of <6 years and those with delays >6 years. Comparison of the pneumonia incidence rates within the stratified groups showed that there were significantly greater numbers of episodes of pneumonia in XLA and CVID patients with delayed diagnoses ($P < 0.003$). Among all the patients, only one 48-year-old CVID patient was a smoker. Four patients with CVID had allergic rhinitis and three had asthma, while none of XLA patients had allergic respiratory disease; therefore, stratification based on smoking and allergic respiratory disease was not necessary.

After immunoglobulin replacement therapy, 15 of 39 XLA patients (38.4%) and 36 of 76 CVID patients (47.3%) had at least one episode of pneumonia; the 15

Table 2 Immunological data for patients with primary antibody deficiency ($n = 115$)

Parameter	XLA	CVID	*P*-value*
WCC ($\times 10^9$/L)	4.79 ± 0.5	8.44 ± 0.46	0.019
Lymphocytes (%)	46 ± 21	35 ± 15	0.05
$CD3^+$ T cell absolute count ($\times 10^9$/L)	3.83 ± 2.19	2.23 ± 1.53	<001
$CD3^+CD4^+$ T cell absolute count ($\times 10^9$/L)	1.70 ± 1.07	0.92 ± 0.66	<001
$CD3^+CD8^+$ T cell absolute count ($\times 10^9$/L)	1.72 ± 1.57	1.18 ± 0.94	0.046
$CD19^+$ B cells (%)	<1	11 ± 5	<0.001
IgG (mg/L)	320 ± 60	1250 ± 120	0.001
IgA (mg/L)	70 ± 50	160 ± 30	0.046
IgM (mg/L)	130 ± 30	260 ± 30	0.31

Data are mean ± SD.
* Calculated by independent *t*-test.
CVID, common variable immunodeficiency; XLA, X-linked agammaglobulinaemia.

Table 3 Respiratory disorders in the patients with primary antibody deficiency ($n = 115$)

Parameter	XLA	CVID	*P*-value
Number of patients with pneumonia (%)			0.03*
Before diagnosis	32 (82)	59 (77.6)	
In patients with delay in diagnosis ≤6 years	29 (90.6)	45 (76.2)	0.01*
In patients with delay in diagnosis >6 years	3 (9.4)	14 (23.8)	0.01*
After diagnosis	15 (38.4)	36 (47.3)	0.43*
Number of episodes of pneumonia (per patient per year)			0.008**
Before diagnosis	59 (1.67)	196 (1.11)	
In patients with delay in diagnosis ≤6 years	24 (1.5)	79 (0.9)	0.001**
In patients with delay in diagnosis >6 years	35 (1.7)	117 (1.2)	0.002**
After diagnosis	22 (0.47)	68 (0.58)	0.07**
Number of patients with abnormal PFT pattern (%)	9 (47.3)	22 (55)	0.07*
Number of patients with bronchiectasis (%)	9 (25)	36 (47)	0.025*
Number of patients with LIP	0	3	0.15*
Number of patients with MALT lymphoma	0	1	0.15*

* Calculated by Pearson's chi-square test.
** Calculated by independent *t*-test.
CVID, common variable immunodeficiency; LIP, lymphoid interstitial pneumonitis; MALT, mucosal-associated lymphoid tissue; PFT, pulmonary function test; XLA, X-linked agammaglobulinaemia.

XLA patients experienced 0.47 episodes of pneumonia per patient per year during follow up, which was not significantly different from the CVID patients, who experienced 0.58 episode of pneumonia per patient per year (Table 3).

Pulmonary function tests

Excluding children under the age of 6 years, who cannot cooperate appropriately for spirometry, PFT was performed for 19 patients with XLA and 40 patients with CVID (Table 3). Nine XLA patients (47%) had abnormal PFT results, with all showing restrictive patterns ($P = 0.002$). Of the CVID patients 22 (55%) showed PFT abnormalities, including eight with restrictive, eight with mixed and six with obstructive patterns. Airway hyperreactivity and asthma were documented in three patients with CVID.

Lung complications

Forty-seven of 115 (41%) patients (38 with CVID and 9 with XLA) developed chronic lung disease. Bronchiectasis was confirmed by HRCT in 9 of 39 (23%) XLA patients, and in 36 of 76 (47%) CVID patients ($P = 0.025$). The characteristics of CVID and XLA patients with bronchiectasis (median age 16 years, range 6–59 years) differed from those of patients without bronchiectasis (median age 5 years, range 1–20 years). The group of patients with bronchiectasis was also older at the time of onset (6 vs 1 month, $P < 0.001$) and at the time of diagnosis (5.4 vs 2 years, $P < 0.001$).

The mean Bhalla score for CVID patients (5) was twice that for the XLA patients (2.5) ($P = 0.004$). Severity of bronchiectasis (9%) and peribronchial thickening (7%) were the most frequently documented HRCT findings in the CVID group. Extensive mucus plugging,

sacculation of abscesses, emphysema and bullae were only observed in the XLA group. During follow up, lymphoid interstitial pneumonitis (LIP) was confirmed in three CVID patients, based on radiological and pathological findings. All three patients showed restrictive patterns on PFT. A diagnosis of lung mucosal-associated lymphoid tissue (MALT) lymphoma was confirmed by lung biopsy in one patient.

DISCUSSION

Recurrent respiratory tract infections, particularly pneumonia, are the most common presenting features of patients with CVID and XLA, which frequently require treatment with i.v. antibiotics and hospitalization. In this series, 59 of 76 CVID patients (77.6%) and 32 of 39 XLA patients (82%) experienced at least one episode of pneumonia before diagnosis. It has been reported that 75–84% of CVID patients[2,24,31,38–40] and 62–82.5% of XLA patients[19,20,22,32] experience at least one episode of pneumonia before diagnosis, while in a substantial proportion of patients, multiple episodes have been reported. Although specific aetiological agents for lower respiratory tract infections were not identified in the present patients, encapsulated bacteria appear to be the most common pathogens isolated from sputum of patients with PAD.[19,38]

The effectiveness of immunoglobulin replacement therapy in reducing the incidence of pneumonia in patients with CVID and XLA is well documented.[30–32,41,42] However, several studies have shown that during patient follow up, respiratory infections remain the most frequent manifestation of the disease.[2,20,22,43–45] In the present series, 36 of 76 CVID patients (47.3%) and 15 of 39 XLA patients (38.4%) experienced at least one episode of pneumonia during the follow-up period. This suggests that other factors besides immunoglobulin deficiency may contribute to the development of recurrent respiratory infections. In order to reduce the frequency of respiratory infections during follow up in PAD patients, further research is needed to define optimal doses of immunoglobulin replacement therapy, and to determine whether prophylactic antibiotic regimens are necessary for appropriate management of this group of patients.

Chronic lung disease, including obstructive, restrictive and bronchiectatic changes, have been documented to develop in a substantial number of patients with PAD. Among these, bronchiectasis and bronchial wall thickening are well-recognized complications, occurring in 7–68% of patients with PAD.[2,20,23,24,26,27,38–40,43,46,47] In the present series, bronchiectasis was documented by HRCT in 23% and 47% of patients with XLA and CVID, respectively. Bronchiectasis is more common in CVID patients than XLA patients, possibly due to long delays in the diagnosis of CVID and the dysregulated immune response that is characteristic of the disease. The present data are in agreement with previous studies showing high rates of bronchiectasis in CVID patients (17–68%),[2,24,27,31,38–40,44] but lower rates in XLA patients (7–24%).[18,21,30,38] Although recurrent infections, delayed diagnosis and inadequate treatment of PAD patients have been implicated as the main causes of structural lung damage and bronchiectasis, some patients develop structural lung damage despite proper management.[2,25,30]

The LIP and MALT lymphomas were detected in three patients and one patient with CVID, respectively. LIP is associated with diffuse or multi-focal reactive lymphoid infiltrates, especially in the alveolar interstitium, and may develop in a subgroup of patients with CVID.[48] Although this condition may have a stable course,[49] progressive deterioration leading to lymphoma has also been reported.[50] MALT lymphoma, a subset of low-grade B cell non-Hodgkin's lymphoma, has also been reported in the lungs of some CVID patients.[51,52] To date, MALT lymphomas and LIP have not been reported in patients with XLA.

Lung defence involves different mechanisms that are necessary for the removal of inhaled particles and organisms. The components of lung defence include those located in the upper airways (e.g. anatomical barriers, the cough reflex and mucociliary clearance), as well as those in the alveoli (e.g. macrophages, humoral factors and cell mediated immunity).[53] Several components of alveolar fluid (e.g. surfactant, fibronectin and CRP) may have opsonic activities.[54] IgG is the predominant immunoglobulin in the alveoli and has potent opsonic activity.[55] Secretory IgA is the first line of adaptive immunity in the upper airways, but is not involved in alveolar immunity.[53,56] Normal alveoli contain about 10% lymphocytes, including $CD4^+$ T cells (50%), $CD8^+$ T cells (30%), natural killer cells (10–15%) and B cells (5%). Both Th1 and Th2 cytokines have important roles in pulmonary defence. Interferon-γ produced by $CD4^+$ T cells, $CD8^+$ T cells, γδ cells and natural killer cells has a central role in microbicidal activity against most intracellular pathogens,[57–61] while Th2 lymphocytes have important roles in some granulomatous diseases.[62] Cell-mediated cytotoxic responses are important in the defence against pulmonary viral infections.[63] It is estimated that about 25% of patients with CVID have moderate $CD4^+$ T lymphopenia, sometimes with a relative expansion of $CD8^+$ T cells. About 30% of patients with CVID have persistently high numbers of circulating $CD8^+$ T cells binding immunogenic peptides from Epstein-Barr virus or cytomegalovirus.[64] In contrast, T lymphocyte numbers and function are normal in patients with XLA.[65]

Patients with CVID who have significantly lower numbers of IgM memory B cells and anti-pneumococcal polysaccharide IgM are at increased risk of developing recurrent bacterial pneumonia and bronchiectasis.[66,67] Measurement of these parameters may alert physicians to the need for more aggressive treatment of these patients. In addition to airway destruction due to repeated infections, genetic polymorphisms may also play a role in the development of bronchiectasis.[68]

It has been estimated that up to 50% of patients with PAD have abnormal spirometry and XLA patients have been reported to have more abnormal lung function than CVID patients.[25] However, in the present study 55% of CVID patients and 47% of XLA

patients had abnormal PFT. A restrictive pattern was the most prevalent on spirometry. This is in contrast to most previous studies that have reported an obstructive pattern to be predominant.[26,27,31,40,69] In one study, up to 40% of CVID patients showed evidence of restrictive disease.[24] A decreased DL_{CO} has been considered an early sign of progression to a restrictive pattern.[40]

In the present study, respiratory infections were more severe and more frequent in XLA patients than in CVID patients before diagnosis (1.67 per patient per year in XLA vs 1.11 per patient per year in CVID), but CVID patients appeared to have a greater likelihood than XLA patients of developing lung disease during the course of the disease. There are two possible reasons for this difference. First, XLA patients are diagnosed earlier than CVID patients because of the more severe and more frequent respiratory infections associated with XLA, whereas the diagnosis of CVID is frequently delayed. Second, in view of the immune dysregulation that occurs in CVID, affected patients may develop inflammatory diseases, such as granulomatous disease and LIP, which could result in more complications in this group of patients.[70]

In conclusion, patients with CVID appear to be at greater risk of developing lung disease compared with those with XLA, possibly because of the earlier diagnosis of XLA patients. In addition, CVID patients are more susceptible to be complicated with lung disease because of a dysregulated immune response. Early diagnosis of patients with PAD and adequate i.v. immunoglobulin replacement therapy substantially reduce the number of pulmonary infections and are the keys to survival and a better quality of life. However, CVID patients are prone to progression of lung disease despite optimal immunoglobulin therapy because of the nature of the disease. This important issue should be addressed in further studies. It is important for physicians to follow up patients with PAD and to obtain baseline PFT data. In addition, HRCT should be considered in patients with chronic chest symptoms in order to monitor lung disease parameters in patients receiving immunoglobulin replacement therapy.

REFERENCES

1 Chapel H, Lucas M, Lee M *et al.* Common variable immunodeficiency disorders: division into distinct clinical phenotypes. *Blood* 2008; **112**: 277–86.
2 Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin. Immunol.* 1999; **92**: 34–48.
3 Di Renzo M, Pasqui AL, Auteri A. Common variable immunodeficiency: a review. *Clin. Exp. Med.* 2004; **3**. 211–17.
4 Aghamohammadi A, Farhoudi A, Moin M *et al.* Clinical and immunological features of 65 Iranian patients with common variable immunodeficiency. *Clin. Diagn. Lab. Immunol.* 2005; **12**: 825–32.
5 Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). *Clin. Immunol.* 1999; **93**: 190–97.
6 Cunningham-Rundles C, Radigan L. Deficient IL-12 and dendritic cell function in common variable immune deficiency. *Clin. Immunol.* 2005; **115**: 147–53.
7 Viallard JF, Camou F, Andre M *et al.* Altered dendritic cell distribution in patients with common variable immunodeficiency. *Arthritis Res. Ther.* 2005; **7**.
8 Kondratenko I, Amlot PL, Webster AD *et al.* Lack of specific antibody response in common variable immunodeficiency (CVID) associated with failure in production of antigen-specific memory T cells. MRC Immunodeficiency Group. *Clin. Exp. Immunol.* 1997; **108**: 9–13.
9 Pozzi N, Gaetaniello L, Martire B *et al.* Defective surface expression of attractin on T cells in patients with common variable immunodeficiency (CVID). *Clin. Exp. Immunol.* 2001; **123**: 99–104.
10 Paccani SR, Boncristiano M, Patrussi L *et al.* Defective Vav expression and impaired F-actin reorganization in a subset of patients with common variable immunodeficiency characterized by T-cell defects. *Blood* 2005; **106**: 626–34.
11 Rezaei N, Aghamohammadi A, Kardar GA *et al.* T-helper 1 and 2 cytokine assay in patients with common variable immunodeficiency. *J. Investig. Allergol. Clin. Immunol.* 2008; **18**: 449–53.
12 Rezaei N, Aghamohammadi A, Siadat SD *et al.* Serum bactericidal antibody responses to meningococcal polysaccharide vaccination as a basis for clinical classification of common variable immunodeficiency. *Clin. Vaccine Immunol.* 2008; **15**: 607–11.
13 Rezaei N, Haji-Molla-Hoseini M, Aghamohammadi A *et al.* Increased serum levels of soluble CD30 in patients with common variable immunodeficiency and its clinical implications. *J. Clin. Immunol.* 2008; **28**: 78–84.
14 Bruton OC. Agammaglobulinemia. *Pediatrics* 1952; **9**: 722–8.
15 Tsukada S, Saffran DC, Rawlings DJ *et al.* Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. *Cell* 1993; **72**: 279–90.
16 Vetrie D, Vorechovsky I, Sideras P *et al.* The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. *Nature* 1993; **361**: 226–33.
17 Conley ME, Broides A, Hernandez-Trujillo V *et al.* Genetic analysis of patients with defects in early B-cell development. *Immunol. Rev.* 2005; **203**: 216–34.
18 Aghamohammadi A, Fiorini M, Moin M *et al.* Clinical, immunological and molecular characteristics of 37 Iranian patients with X-linked agammaglobulinemia. *Int. Arch. Allergy Immunol.* 2006; **141**: 408–14.
19 Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: an analysis of 96 patients. *Medicine (Baltimore)* 1985; **64**: 145–56.
20 Plebani A, Soresina A, Rondelli R *et al.* Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicenter study. *Clin. Immunol.* 2002; **104**: 221–30.
21 Moin M, Aghamohammadi A, Farhoudi A *et al.* X-linked agammaglobulinemia: a survey of 33 Iranian patients. *Immunol. Invest.* 2004; **33**: 81–93.
22 Winkelstein JA, Marino MC, Lederman HM *et al.* X-linked agammaglobulinemia: report on a United States registry of 201 patients. *Medicine (Baltimore)* 2006; **85**: 193–202.
23 Dukes RJ, Rosenow EC 3rd, Hermans PE. Pulmonary manifestations of hypogammaglobulinaemia. *Thorax* 1978; **33**: 603–7.
24 Watts WJ, Watts MB, Dai W *et al.* Respiratory dysfunction in patients with common variable hypogammaglobulinemia. *Am. Rev. Respir. Dis.* 1986; **134**: 699–703.
25 Sweinberg SK, Wodell RA, Grodofsky MP *et al.* Retrospective analysis of the incidence of pulmonary disease in hypogammaglobulinemia. *J. Allergy Clin. Immunol.* 1991; **88**: 96–104.
26 Kainulainen L, Varpula M, Liippo K *et al.* Pulmonary abnormalities in patients with primary hypogammaglobulinemia. *J. Allergy Clin. Immunol.* 1999; **104**: 1031–6.
27 Thickett KM, Kumararatne DS, Banerjee AK *et al.* Common variable immune deficiency: respiratory manifestations, pulmonary

function and high-resolution CT scan findings. *QJM* 2002; **95**: 655–62.
28 Park JE, Beal I, Dilworth JP *et al.* The HRCT appearances of granulomatous pulmonary disease in common variable immune deficiency. *Eur. J. Radiol.* 2005; **54**: 359–64.
29 Aghamohammadi A, Pouladi N, Parvaneh N *et al.* Mortality and morbidity in common variable immunodeficiency. *J. Trop. Pediatr.* 2007; **53**: 32–8.
30 Quartier P, Debre M, De Blic J *et al.* Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J. Pediatr.* 1999; **134**: 589–96.
31 Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. *J. Allergy Clin. Immunol.* 2002; **109**: 1001–4.
32 Aghamohammadi A, Moin M, Farhoudi A *et al.* Efficacy of intravenous immunoglobulin on the prevention of pneumonia in patients with agammaglobulinemia. *FEMS Immunol. Med. Microbiol.* 2004; **40**: 113–18.
33 Garner JS, Jarvis WR, Emori TG *et al.* CDC definitions for nosocomial infections, 1988. *Am. J. Infect. Control* 1988; **16**: 128–40.
34 American Thoracic Society. Standardization of spirometry—1987 update. Statement of the American Thoracic Society. *Am. Rev. Respir. Dis.* 1987; **136**: 1285–98.
35 Bhalla M, Turcios N, Aponte V *et al.* Cystic fibrosis: scoring system with thin-section CT. *Radiology* 1991; **179**: 783–8.
36 Grenier P, Cordeau MP, Beigelman C. High-resolution computed tomography of the airways. *J. Thorac. Imaging* 1993; **8**: 213–29.
37 Hansell DM, Wells AU, Rubens MB *et al.* Bronchiectasis: functional significance of areas of decreased attenuation at expiratory CT. *Radiology* 1994; **193**: 369–74.
38 Hermaszewski RA, Webster AD. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. *Q. J. Med.* 1993; **86**: 31–42.
39 Kainulainen L, Nikoskelainen J, Ruuskanen O. Diagnostic findings in 95 Finnish patients with common variable immunodeficiency. *J. Clin. Immunol.* 2001; **21**: 145–9.
40 Martinez Garcia MA, de Rojas MD, Nauffal Manzur MD *et al.* Respiratory disorders in common variable immunodeficiency. *Respir. Med.* 2001; **95**: 191–5.
41 Pourpak Z, Aghamohammadi A, Sedighipour L *et al.* Effect of regular intravenous immunoglobulin therapy on prevention of pneumonia in patients with common variable immunodeficiency. *J. Microbiol. Immunol. Infect.* 2006; **39**: 114–20.
42 Bayrakci B, Ersoy F, Sanal O *et al.* The efficacy of immunoglobulin replacement therapy in the long-term follow-up of the B-cell deficiencies (XLA, HIM, CVID). *Turk. J. Pediatr.* 2005; **47**: 239–46.
43 Hermans PE, Diaz-Buxo JA, Stobo JD. Idiopathic late-onset immunoglobulin deficiency. Clinical observations in 50 patients. *Am. J. Med.* 1976; **61**: 221–37.
44 Hausser C, Virelizier JL, Buriot D *et al.* Common variable hypogammaglobulinemia in children. Clinical and immunologic observations in 30 patients. *Am. J. Dis. Child.* 1983; **137**: 833–7.
45 Pettit SJ, Bourne H, Spickett GP. Survey of infection in patients receiving antibody replacement treatment for immune deficiency. *J. Clin. Pathol.* 2002; **55**: 577–80.
46 Obregon RG, Lynch DA, Kaske T *et al.* Radiologic findings of adult primary immunodeficiency disorders. Contribution of CT. *Chest* 1994; **106**: 490–95.
47 Rezaei N, Aghamohammadi A, Moin M *et al.* Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: update from the Iranian Primary Immunodeficiency Registry. *J. Clin. Immunol.* 2006; **26**: 519–32.
48 Buckley RH. Pulmonary complications of primary immunodeficiencies. *Paediatr. Respir. Rev.* 2004; **5** (Suppl A): S225–33.
49 Levinson AI, Hopewell PC, Stites DP *et al.* Coexistent lymphoid interstitial pneumonia, pernicious anemia, and agammaglobulinemia. *Arch. Intern. Med.* 1976; **136**: 213–16.
50 Kohler PF, Cook RD, Brown WR *et al.* Common variable hypogammaglobulinemia with T-cell nodular lymphoid interstitial pneumonitis and B-cell nodular lymphoid hyperplasia: different lymphocyte populations with a similar response to prednisone therapy. *J. Allergy Clin. Immunol.* 1982; **70**: 299–305.
51 Aghamohammadi A, Parvaneh N, Tirgari F *et al.* Lymphoma of mucosa-associated lymphoid tissue in common variable immunodeficiency. *Leuk. Lymphoma* 2006; **47**: 343–6.
52 Cunningham-Rundles C, Cooper DL, Duffy TP *et al.* Lymphomas of mucosal-associated lymphoid tissue in common variable immunodeficiency. *Am. J. Hematol.* 2002; **69**: 171–8.
53 Nicod LP. Pulmonary defence mechanisms. *Respiration* 1999; **66**: 2–11.
54 O'Neill SJ, Lesperance E, Klass DJ. Human lung lavage surfactant enhances staphylococcal phagocytosis by alveolar macrophages. *Am. Rev. Respir. Dis.* 1984; **130**: 1177–9.
55 Reynolds HY, Newball HH. Analysis of proteins and respiratory cells obtained from human lungs by bronchial lavage. *J. Lab. Clin. Med.* 1974; **84**: 559–73.
56 Laurenzi GA, Potter RT, Kass EH. Bacteriologic flora of the lower respiratory tract. *N. Engl. J. Med.* 1961; **265**: 1273–8.
57 Cooper AM, Dalton DK, Stewart TA *et al.* Disseminated tuberculosis in interferon gamma gene-disrupted mice. *J. Exp. Med.* 1993; **178**: 2243–7.
58 Belkaid Y, Rouse BT. Natural regulatory T cells in infectious disease. *Nat. Immunol.* 2005; **6**: 353–60.
59 Hayday A, Tigelaar R. Immunoregulation in the tissues by gammadelta T cells. *Nat. Rev. Immunol.* 2003; **3**: 233–42.
60 Isogai S, Jedrzkiewicz S, Taha R *et al.* Resident CD8+ T cells suppress CD4+ T cell-dependent late allergic airway responses. *J. Allergy Clin. Immunol.* 2005; **115**: 521–6.
61 Curtis JL. Cell-mediated adaptive immune defense of the lungs. *Proc. Am. Thorac. Soc.* 2005; **2**: 412–16.
62 Chensue SW, Terebuh PD, Warmington KS *et al.* Role of IL-4 and IFN-gamma in Schistosoma mansoni egg-induced hypersensitivity granuloma formation. Orchestration, relative contribution, and relationship to macrophage function. *J. Immunol.* 1992; **148**: 900–6.
63 Wyde PR, Cate TR. Cellular changes in lungs of mice infected with influenza virus: characterization of the cytotoxic responses. *Infect. Immun.* 1978; **22**: 423–9.
64 Webster AD. Clinical and immunological spectrum of common variable immunodeficiency (CVID). *Iran. J. Allergy Asthma. Immunol.* 2004; **3**: 103–13.
65 Ochs HD, Smith CI. X-linked agammaglobulinemia. A clinical and molecular analysis. *Medicine (Baltimore)* 1996; **75**: 287–99.
66 Vodjgani M, Aghamohammadi A, Samadi M *et al.* Analysis of class-switched memory B cells in patients with common variable immunodeficiency and its clinical implications. *J. Investig. Allergol. Clin. Immunol.* 2007; **17**: 321–8.
67 Carsetti R, Rosado MM, Donnanno S *et al.* The loss of IgM memory B cells correlates with clinical disease in common variable immunodeficiency. *J. Allergy Clin. Immunol.* 2005; **115**: 412–17.
68 Sansom ME, Ferry BL, Sherrell ZP *et al.* A preliminary assessment of alpha-1 antitrypsin S and Z deficiency allele frequencies in common variable immunodeficiency patients with and without bronchiectasis. *Clin. Exp. Immunol.* 2002; **130**: 489–94.
69 Bates CA, Ellison MC, Lynch DA *et al.* Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. *J. Allergy Clin. Immunol.* 2004; **114**: 415–21.
70 Tanaka N, Kim JS, Bates CA *et al.* Lung diseases in patients with common variable immunodeficiency: chest radiographic, and computed tomographic findings. *J. Comput. Assist. Tomogr.* 2006; **30**: 828–38.