

# The pulmonary complications during the course of CVID

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## Abstract

*This review gives particular emphasis to the frequency of pulmonary complications during the course of common variable immunodeficiency (CVID). The most frequent are chronic pneumonitis, bronchiectasis and parenchymal lung diseases. In patients with CVID syndrome, delay in lung disease recognition is frequent. This results in derangement of the lung structure and loss of functional tissue. Therefore important clinical information has been available concerning current diagnostic processes. These studies conclude that early diagnosis make possible the effective treatment.*

**Key words:** CVID, lung diseases, bronchiectasis, interstitial, diagnosis, treatment.

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## Introduction

Common variable immunodeficiency (CVID) is characterized by abnormal humoral response, accompanied by immunoglobulin deficiency [1, 2]. Patients with CVID suffer from recurrent and often chronic infections, these can cause pulmonary changes [3, 4]. The most frequently observed CVID complications within the respiratory tract are bronchiectasis, interstitial disorder, granulomas and lymphomas [5]. Mechanisms leading to development of chronic pulmonary changes have not been thoroughly researched.

Lungs are subjected to constant contact with various antigens. Patients with CVID harbour viral and bacterial infections, which may predispose to the development of changes in the lower respiratory tract [3]. The lungs defence mechanisms eliminate foreign bodies through spontaneous, local mechanisms or through immunological reactions. Lymphoid tissue of the respiratory tract is located within the lymph nodes (such as peribronchiolar, trachea and hilar lymph nodes) as well as accumulating in lymphoid tissue, the lining the bronchi, submucosal areas, in interalveolar septa and in alveoli. Clusters of lymphoid follicles and also solitary lymphoid follicles (bronchus-associated lymphoid tissue - BALT), are frequently found within mucosa and submucosa of the respiratory tract. Most immunoglobulins found in the

respiratory tract are produced locally. IgA is mainly to be found in the large bronchi, and lower airways are dominated by IgG. Other essential elements of the immune system are epithelial cells of the bronchi, with MHC class I and class II molecules on their surface. These cells also secrete chemotactic factors and antyproteases. The alveolar macrophages have several functions including phagocytosis.

## Pulmonary changes associated with CVID

The reason responsible for changes in lung parenchyma during immunological disorder have not been completely explained. Pulmonary changes may be the result of either of the following: chronic presence of virus antigen or bacteria, or through cytokine activity and/or circulating lymphocytes influx. Various different genetic disorders may bring about pulmonary changes [6-8]. Parenchymal lung diseases consist of many CVID complications and are 240 times more frequent in patients with immunoglobulin deficiency than in remaining population [9]. The results of large series of 103 patients with CVID have shown, that 22% patients were diagnosed with pulmonary changes (regardless of the presence bronchiectasis) [10]. The varied syndromes appear in the lungs, in which alveoli and tissue around alveoli become inflamed by immune cells.

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Progression of the disease leads to disseminated infiltrates in lungs, fibrosis and lung structure remodelling. Increasing changes within the lungs lead to gas exchange disorders (especially restrictive), further to pulmonary hypertension and complications in the circulatory system.

On the basis of American Thoracic Society/ European Respiratory Society consensus (2001), thoroughly defined and classified diffuse parenchymal lung disease (DPLD) as the following: 1. DPLD of known cause e.g. drugs or association e.g. collagen vascular disease; 2. Idiopathic interstitial pneumonias; 3. Granulomatous DPLD e.g. sarcoidosis; 4. Other forms of DPLD e.g. histiocytosis X etc [11].

The relationship between dysgammaglobulinemia and interstitial lung diseases was described for the first time by Liebow and Carrington in 1973. The authors thoroughly investigated 18 cases of lymphocytic interstitial pneumonia (LIP) of which: 8 patients with hypergammaglobulinemia IgG, 4 patients with hypergammaglobulinemia IgM and 5 patients with hypogammaglobulinemia were observed [12]. Other authors obtained similar results [13, 14]. The presence of LIP in patients with common variable immunodeficiency has been well documented [15-17]. The origin of lymphoproliferation has yet to be fully investigated. Regardless of agent evoking abnormal immune responses, under observation patients with LIP have enlarged cervical, thoracic and abdominal lymph nodes [16]. Infiltration by small, mature, polyclonal lymphocytes and plasma cells diffused in lung parenchyma, as well as enlarged lymph nodes, within the lung, resemble huge lymphoid organ. Splenomegaly is often accompanied by enlarged Peyer's patches within the intestinal wall. Occasionally cells also infiltrating other organs can be observed [18, 19]. Benign lymphoproliferative disorders are recognised in about 30% of patients with CVID. They are often accompanied by splenomegaly and lymphadenopathy. Such patients are particularly susceptible to lymphoma, when mixed B and T lymphocytes are present [20]. Other uncommon idiopathic interstitial pneumonias have also been observed in patients with CVID [21, 22].

Previous studies demonstrated, that in patients with firstly diagnosis of low immunoglobulin serum levels, the lung disease can develop or secondly immunological disorder manifestations, occurring during the course of the lung disease. Among a series of 47 patients with CVID, out of which 89% were diagnosed with following lung diseases (based on lung function and high-resolution computed tomography findings): bronchiectasis (68% of patients), asthma (15%), recurrent pneumonia (19%) and granulomatous lung disease (4%) [23]. Within the another series of 69 cases of CVID syndrome, 35% of patients had chronic respiratory symptoms (without diffuse radiographic abnormalities) and 26% had chronic respiratory symptoms and diffuse radiographic abnormalities. Results of this clinical evaluation revealed that 13 patients had syndromes referred to as granulomatous-lymphocytic interstitial lung

disease, (such as: granulomatous lung disease, lymphocytic interstitial pneumonia, follicular bronchiolitis, and lymphoid hyperplasia) and 5 patients suffered from other interstitial lung diseases. This study revealed that 58% patients with CVID developed the following symptoms: non-infectious lung complications, dyspnea, splenomegaly, restrictive pulmonary physiology, consolidation, ground-glass attenuation, and reticular radiographic abnormalities, along with low CD3+ and CD8+ cell populations [24].

The observations of changes occurring in lungs are uncommon due to intravenous immunoglobulin replacement therapy. In the case series of 19 patients with CVID, the mean duration of replacement therapy was 7.5 years. Bronchiectasis were diagnosed in 58% patients and 42% had multi-lobar bronchiectasis. Chronic airflow limitation were present in 53% patients and in one case a restrictive pattern was observed [25]. In another series of 22 patients, high-resolution computed tomography (HRCT) shown pulmonary abnormalities in 21 patients (18 patients had common variable immunodeficiency). Bronchiectasis were present in 72% of patients (whereas chest radiographs revealed bronchiectasis in only 13% of patients). A prospective 3-year follow-up showed progression in 30% of patients who were received intravenous immunoglobulin replacement therapy [1].

A large series of patients with pulmonary changes, during the course of the illness were diagnosed with immunological disorders. Among the group of 148 cases with recurrent respiratory tract infections, 19% of patients were diagnosed with hypogammaglobulinemia IgG. In 8 of patients pulmonary changes were accompanied with CVID. Within the group of patients who had CVID syndrome, the following was recognised: 2 patients with cryptogenic organising pneumonia (COP), 1 with usual interstitial pneumonia (UIP), 2 with chronic pneumonitis, 1 with bronchiolitis and fibrosis and peripheral tags in further 2 patients [9]. Other studies recognised CVID in 7 adults with respiratory diseases (6 patients – bronchiectasis; 2 patients – tuberculosis) [26].

Many cases of CVID are accompanied by noncaseating granulomas [27-30]. One of such disease coexisting with CVID syndrome is sarcoidosis. A series of well-documented medical histories of 8 patients with sarcoidosis and CVID were presented, as well as summary of the previously reported 22 cases of sarcoidosis accompanying CVID syndrome [31]. Other authors obtained similar results. In a group of 189 patients diagnosed with CVID, 17 cases of granulomatous lesions discovered in lung tissue biopsy. The length of time between finding granulomas (with or without lung disease) and the institution of treatment with immunoglobulin replacement therapy, ranged from 2 to 17 years [27].

Unfortunately, the knowledge of CVID symptoms by general practitioners, respiratory physicians and paediatricians is insufficient. Often the correct diagnosis is given only after the patient has experienced long periods suffering with lung

disease. In National Institute for Tuberculosis and Lung Diseases in Warsaw between 1987-2002, 35 patients with lung disease were diagnosed with CVID. The average waiting time between symptoms and correct diagnosis has often exceeded 8 years [32]. Research into sarcoidosis revealed that in 36% of patients the first diagnosis was lung disease and later recognised CVID syndrome, ranging from 1-15 years (average of 4.7 years). In 36% of patients, sarcoidosis and CVID syndrome have been recognised concurrently [31]. In another series, diagnosis of sarcoidosis preceded CVID recognition by 2-17 years (an average 9.5 years) in 41 % of patients [27].

On the other hand, in patients with CVID syndrome, there is delay in lung disease recognition [16, 33]. In one published series, in 47% of patients with CVID syndrome the mean time between the first symptoms and actual diagnosis of lung disease was 8.7 years. The mean time difference between pulmonological and immunological diagnoses was 5 years [23]. Another series reported similar findings in 23% of patients, CVID was recognised about 3.5 years prior to diagnosis of lungs changes [27]. Among patients with sarcoidosis, in 20% of cases CVID was recognised about 4 years prior to the recognition of lung disease [31]. Other studies have concurrent findings.

### **Pulmonary interstitial changes in children with CVID**

Within the period of a child's development the disease progress in the immature lungs, thus character and the process of the disease, as well as clinical importance of histological changes in lungs are different than in adults. Classification of chronic interstitial lung diseases in immunocompetent children was for the first time scientifically described by European Respiratory Society in 2004. Previous reports, even from large health service centres, focused only on a small groups of children [34]. Diffuse parenchymal lung disease (DPLD) in children was divided into 4 groups: 1.DLPD of unknown association, 2.idiopathic interstitial pneumonitis, 3.other forms of interstitial pneumonia, 4.congenital disorder. This classification did not include lung diseases in children with immunodeficiency. Thus, information about the development of the disease, diagnosis and treatment is based on these rare case reports [35].

An assessment of the value of HRCT was carried out in determining the extent and significance of lung diseases, among a large group of children with antibody deficiency disorders over a 5-year period, this showed that HRCT is useful to demonstrating the extent and severity of lung disease in diagnosis and during therapy. Among 37 children of this group, 22 had changes in computed tomography (CT) lung scans, 9 children were diagnosed with bronchiectasis. There were positive relationship between the effects of intravenous immunoglobulin replacement therapy (IVIG), along with

pulmonary function tests. The researchers assessed correlation between CT scores and clinical factors, also including age at the time of diagnosis, age of CT and the progress of the lung disease [36].

The interpretation difficulties of histopathological examination of the lung tissue biopsy samples in the growth and development period are unanimously well-known [37, 38]. The case reports presenting interstitial lung changes, particularly in children with immunodeficiency diseases, are rare. The results of histopathological examinations of lung biopsy of 27 children with interstitial lung disease revealed 2 children with diagnosis of immunological disorder: a 12-year-old patient with CVID (the result of histopathological examination was LIP), and a 3-year-old boy with hypogammaglobulinaemia (the result of histopathological examination was follicular bronchiolitis) [38].

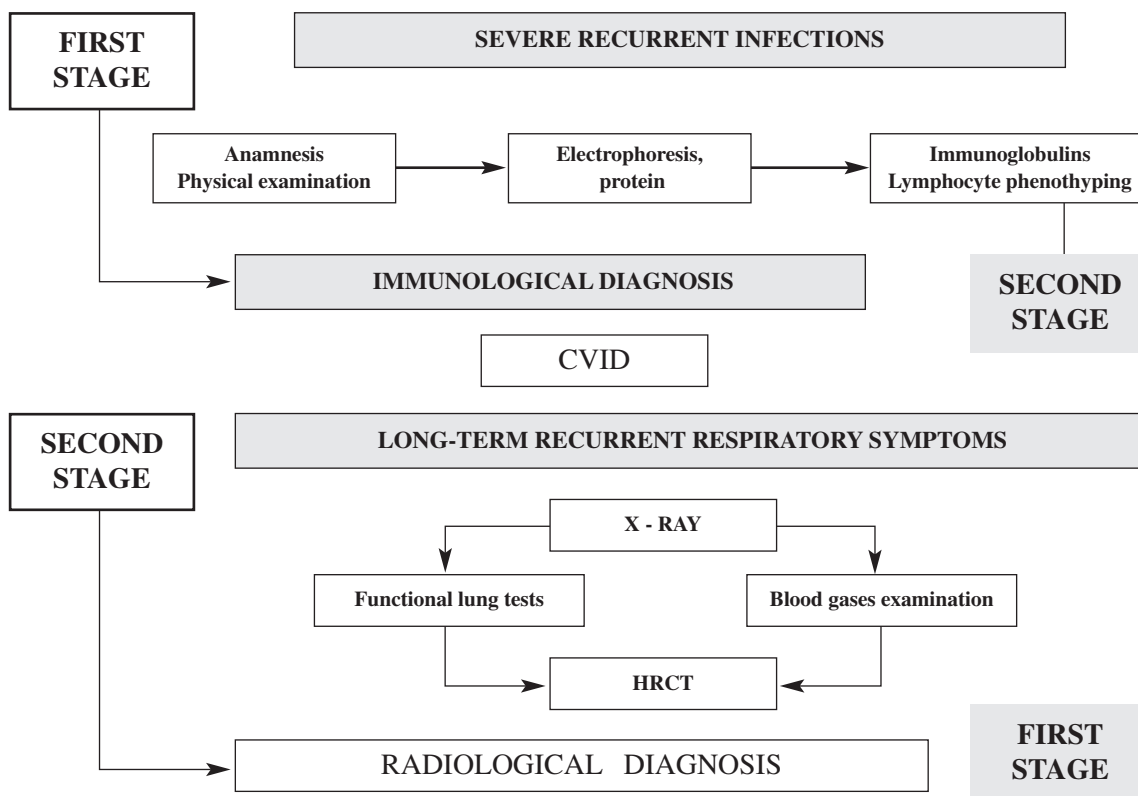
### **Clinical manifestation of the disease**

The most common presentation of lung diseases during the CVID are common follow symptoms: breathlessness cough, fever, tachypnoe/dyspnoe, chest pain, perspiration, anorexia, weight loss, and difficulties in physical intensive effort. A number of patients, particularly children, are treated with the assumption that this disease is asthma. The fine crackles, lymphadenopathy, hepatosplenomegaly and later clubbing, are common symptoms in physical examination [9, 24, 31].

The recurrent and progressive course of disease caused to dyspnoe, respiratory and circulatory failure. Finally consecutive infection leads to the death of the patients.

### **Diagnostics of pulmonary changes during the course of CVID**

The diagnosis of lung disease is based on: functional, radiological and histopathological examination of the lungs. When advanced pulmonary parenchymal changes are recognised, hypoxia is diagnosed. After a patient undergoes physical exercise further examinations can be conducted of blood gases and DL<sub>CO</sub> tests. The data reveals changes and differences between bronchoalveolar lavage (BAL) results in various lung diseases. According to the research BAL and HRCT examination provide conclusive findings when combined and compared during a process of elimination. A number of authors suggest, that new clinical markers must be found (for both diagnosis and prognosis) in order to characterise BAL cells in interstitial lung diseases [39]. Transbronchial biopsy may prove helpful only in some diseases associated with CVID. X-ray examination in patients who have CVID may reveal: bronchiectasies, interstitial changes (especially in the lower parts of lungs), enlarged hilar and/or mediastinal lymph nodes. However, X-ray are not always able to detect the presence of the



**Fig. 1.** Stage I presents immunological diagnostics; stage II – pulmonological diagnostics. First diagnosis dictates the particular order of examinations. In patients with CVID who have respiratory symptoms, the next stage is diagnostic process of the lung. Patients who are diagnosed with lung disease and suffering from recurrent severe infections, should have an immunological examination as the next stage

disease. An X-ray with no abnormalities may be taken even when the disease is presently active [40, 33].

An essential examination of parenchymal lung diseases is high-resolution computed tomography. This disease may result in: regions of lung consolidation (especially subpleural), thickening of interlobar septa and of the airway walls, bronchiectasis, sometimes ground glass attenuation, reticular opacity and honeycombing caused by fibrosis. In patients with bronchiectasis or with symptoms of fibrosis (especially in UIP), HRCT is often the final examination confirming the diagnosis. HRCT is also helpful in both, evaluating the course of the disease as well as therapy [36]. A lung biopsy is required in almost all cases of interstitial lung disease to achieve correct diagnosis. Surgical biopsy in CVID patients has added risks and can cause complications. When a disease is well-documented in HRCT, such as pulmonary fibrosis, a biopsy is performed only in 12-20% patients [26]. However, for final clinicopathologic diagnosis, a histological examination is necessary, if accurate diagnosis can not be established by non-invasive methods [11]. Experienced pathomorphologist

should examine the lung biopsy specimen. Histological features usually reveal: cellular infiltration in interstitial lung tissue, progressive destruction of lung structure and various levels of fibrosis. Sometimes for definitive diagnosis, even immunohistochemical examination is also necessary. It is essential to differentiate between polyclonal and monoclonal cells infiltration.

We have attempted to arrange the diagnostic process in ordered stages, in patients with CVID and pulmonary complications (figure 1).

### Treatment

These rare case reports, serve as the source only of information regarding treatment of lung diseases accompanying CVID. The patients suffering from CVID undergo intravenous immunoglobulin replacement therapy [31, 36, 40]. In patients with accompanying pulmonary parenchymal changes it is advisable to administer prednisone (in doses of 0.5-1 mg/kg day, not exceeding 100 mg/day) [15]. In children, treatment with pulsed

methylprednisolone is recommended (in doses of 10-30 mg/kg/day for three days consecutively at monthly intervals) [34]. The treatment should last for 6-12 weeks and after this period daily doses should be reduced gradually until full remission. When the recurrence of pulmonary changes are observed, immunosuppressive therapy (chlorambucil, cyclosporine) or a combination of both (prednisone and cyclosporine) is recommended [16, 33]. In a few cases where CVID accompanied sarcoidosis, IVIG therapy led to regression of pulmonary changes [41].

Due to a relatively small number of observations and wide ranges of treatments schemes, it is difficult to evaluate long-term effects of therapy. Generally, development of the disease leads to gradual destruction of lung tissue and disturbances in lung architecture. Also cases of spontaneous recovery have also been observed.

## Conclusion

This review gives particular emphasis to pulmonary complications caused by CVID. Important clinical information has now been available concerning current diagnostic processes and disease limitation management. Patients with immunodeficiency are susceptible to severe and long-term infections. The most frequent of these, are chronic pneumonitis and bronchitis which, when recurrent, lead to bronchiectasis. The findings presented throughout this report show, that bronchiectasis are present within 68%-78% of adult patients with both CVID and chronic pneumonitis [1, 23] along with 24% of children [36]. The further progression of bronchiectasis was observed in only 30% of adult patients, who received intravenous immunoglobulin replacement therapy [1].

However, etiology of parenchymal lung diseases associating CVID are yet not clear, the interstitial and alveoli lesions are often observed. The most frequent are interstitial lung diseases and granulomas (e.g. sarcoidosis). Considerable delay in diagnosis of the lung disease accentuated the course of CVID. The probable cause of late recognition could be due to a long drawn out diagnostic process as well as the small knowledge of specialists in this range. This results in irreversible changes in lungs, such as: bronchiectasis, progressive derangement of alveoli architecture, fibrosis and loss of functional tissue. The prognosis is reliable so long as the diagnosis made early and further to this suitable therapy is recommended.

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