

## Case Report

# Common variable immunodeficiency disorder associated with bronchiectasis: a case report

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## ABSTRACT

Common variable immunodeficiency disorder (CVID) is the commonest type of primary immunodeficiency disorders (PIDs) characterized by hypogammaglobulinemia, defective specific antibody production and increased susceptibility of recurrent infections. Autoimmunity, neoplasm and lymphoproliferative disorders are usually associated with CVID. In most cases, the cause is unknown, but multiple gene mutations (10%) may be associated with CVID. Here, we report an eight years old girl with CVID presented with recurrent infections, growth failure, generalized lymphadenopathy and hepatosplenomegaly. Chest examination and radiological findings of this girl were consistent with bronchiectasis. Lack of awareness among health care providers is the reason for delayed diagnosis of several years for this girl. Therefore, it is essential to raise awareness regarding PID patients among the physicians to improve the quality of life.

**Keywords:** CVID, Hypogammaglobulinemia, Recurrent infections

## INTRODUCTION

Common variable immunodeficiency disorders (CVIDs) are the most common type of PIDs in children after four years of age. Patients with CVID also have an increased incidence of autoimmunity, lymphoproliferative disorders and malignancies.<sup>1</sup> CVID affects males and females equally. It has an estimated prevalence ranging from 1:10,000 to 1:50,000. The clinical spectrum of CVID is broad, and it may present at any age. Peaks of presentations are found in the childhood and early adult life. An average delay of 4–6 years between the onset of symptoms and diagnosis was observed.<sup>2</sup>

There is no single immunological or genetic test for diagnosis of CVID. It may be defined by the following criteria:<sup>3</sup> 1) serum IgG must be <2 standard deviations

below the age-adjusted norms with low IgA and or IgM levels 2) poor or absent response to immunization, antigen or natural infection.

CVIDs are diagnoses of exclusion of all known causes of inadequate antibody production or with low serum immunoglobulin levels.<sup>1</sup> The hallmark of immune defect in CVID is failed B cell differentiation with impaired secretion of immunoglobulin. The number of B cells may be normal or decreased (13%), reduced helper T cell, toll-like receptor, and B cells' switching, resulting in impaired primary and secondary immune responses.<sup>3</sup>

In CVID, patients usually present with recurrent respiratory tract infections (sinusitis, otitis media and pneumonia), frequent diarrhea with *Giardia* or *Campylobacter* infection and malabsorption. Bacterial skin infection, urinary infection, sepsis and opportunistic

infections (candidiasis, herpes zoster, tuberculosis, cytomegalovirus) were also reported in the literature.<sup>4</sup>

Bronchiectasis is a common respiratory problem with varied etiology and CVID is not an uncommon cause for this. Bronchiectasis has been reported in 17-76 % of CVID patients.<sup>5</sup> Repeated infections induce chronic inflammation, progressive damage of the bronchial wall, dilatation and bronchus remodeling leading to Bronchiectasis. Frequent hospitalization and inadequate response to antibiotics resulting from progressive pulmonary function deterioration are the essential features found in these patients.<sup>6</sup>

Here we report an eight years old girl with CVID presenting with recurrent infection, failure to thrive, lymphadenopathy and hepatosplenomegaly. She also had Bronchiectasis evidenced by both clinical and imaging basis. Delayed referral and diagnosis in this index case demands increased awareness of PID cases among the physicians.

## CASE REPORT

An eight years old girl, second issue of a non-consanguineous parent, admitted in the department of Paediatrics of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, with high grade, continued fever and productive cough for ten days in February 2020. She also developed breathing difficulty for the last three days before admission. She had history of several diarrheal episodes, ear infections and pneumonia since her four years of age. For these reasons, she was admitted into different hospitals several times and treated with intravenous antibiotics and other supportive measures. There was no history of immunodeficiency in her family.

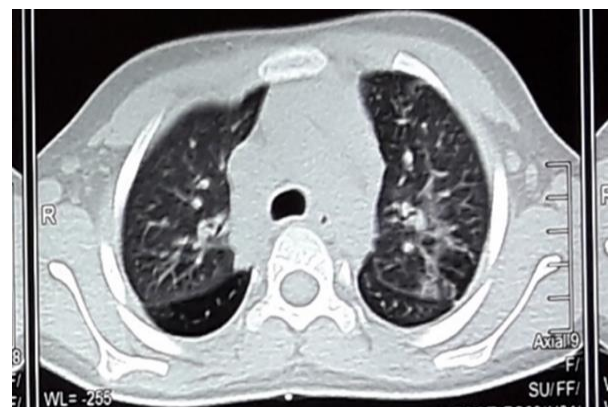
On examination, she had mild pallor, clubbing, generalized lymphadenopathy and growth failure (WAZ: -2.6, HAZ: -3.7). She was febrile and dyspneic. BCG mark was absent and tonsils were visible. Chest examination revealed features of consolidation in the left lung evidenced by decreased chest movement, dull on percussion and breath sound reduced in the left side. Moderate hepatosplenomegaly was present. Other systemic examinations were normal. Laboratory findings showed low Hb (10.8 g/dl), high ESR (90 mm in 1st hr), neutrophilic leukocytosis (TC: 21,850/mm<sup>3</sup>, N-80%) and normal platelet count. S. electrolytes, SGPT, S creatinine, stool routine and fat analysis were normal. Quantitative immunoglobulin assay revealed low IgG: 1.29 gm/l (normal range: 4.2-16.82 gm/l) and IgA: 0.262 gm/l (normal range: 0.7-4.00 gm/l) but normal IgM: 3.2 gm/l (normal range: 0.38-3.51 gm/l). Specific antibody responses were poor in this girl, evidenced by low blood group antibody: (anti B titers 1:64), and low anti-measles antibody (<100mIU/ml) and poor anti-HBs response (0.105 mIU/ml). Lymphocyte subset analysis by flow cytometry was normal. Coomb's test was found negative and the sweat chloride test was normal. Chest x-ray

showed homogenous opacity in the left lung field (Figure 1). High resolution Computed Tomography scan (HRCT) showed thickening of the bronchial wall with tortuosity of bronchioles suggestive of bilateral bronchiectasis (Figure 2).

From the above scenario, this girl was diagnosed as a case of CVID with bronchiectasis. She was managed initially with intravenous antibiotics and with other supportive measures. Intra venous immunoglobulins (IVIG) was given 400 mg/kg during admission and then at regular four-weekly intervals. Prophylactic antibiotics (penicillin, cotrimoxazole and azithromycin) were given to prevent recurrent infections. She was discharged after one month of hospital staying. After that she was regularly attending the follow-up clinic and maintained good health.



**Figure 1: CXR showing homogenous opacity (consolidation) in the left lung field.**



**Figure 2: HRCT showing bilateral bronchiectasis.**

## DISCUSSION

CVIDs include a group of clinically and genetically heterogeneous disorders that arise from B and T lymphocyte dysfunctions. CVIDs are mostly sporadic and inherited conditions (20%), also found as autosomal dominant and autosomal recessive forms.<sup>2,7</sup> In the recent years, an attempt to identify the gene responsible for CVIDs observed defects in the following genes: TACI

(transmembrane activator, calcium modulator and cyclophilin ligand interactor), ICOS (inducible co-stimulator), CD19 and BAFFR (B cell activating factor receptor).<sup>8</sup> Nowadays, these genetic mutations seen in CVID patients are known as monogenic defects.<sup>9</sup>

CVID patients usually present with recurrent skin, respiratory, gastrointestinal, ear and sinus infections. Usually, these patients also have growth failure, organomegaly and lymphadenopathy. Lab findings show low immunoglobulin level (at least two; low IgG and IgA) and inadequate response to vaccination or natural infections.<sup>6</sup> Kokron et al in their Brazilian study, observed that CVID patients present clinically with relevant signs and symptoms, low serum IgG and IgA and reduced T and B lymphocyte count in the blood. Additional criteria include low or absent isohemagglutinins and poor antibody response to vaccines.<sup>4</sup> We also found similar findings except T and B lymphocyte count, which were found normal in our case. Most CVID patients have the normal number of B lymphocytes, and approximately 50% of them have normal T lymphocytes which was present in this case.<sup>2</sup>

Many conditions with hypogammaglobulinemia present with recurrent infections, therefore it is essential to exclude other well-defined causes of hypogammaglobulinemia in the suspected cases. Besides, there is no definitive immunological or genetic test for the diagnosis of CVID. X-linked agammaglobulinemia (XLA) and X-linked lymphoproliferative (XLP) syndrome usually present shortly after birth, whereas CVID is often manifested after four years of age.<sup>6,10</sup> In this case, T was a girl who had tonsils, generalized lymphadenopathy, low IgG, IgA in the presence of normal B and T cell count and impaired antibody production, which was very much suggestive for CVID. The average number of NK cells and no history of EBV infection in this girl also excluded XLP syndrome. Low IgG, IgA in the presence of normal IgM also excluded hyper IgM syndrome in our case.

Infections of the lower respiratory tract (recurrent pneumonia) often result in bronchiectasis. Bronchiectasis is a late manifestation in CVID and indicates repetitive infective insults. HRCT scan is the single best imaging tool for diagnosing and monitoring bronchiectasis in CVID.<sup>11</sup> An Indian study reported a CVID patients presented with fever, chest pain, cough with purulent expectoration, and increased breathlessness. Chest radiograph and HRCT were suggestive of bilateral diffuse bronchiectasis.<sup>5</sup> We also found similar findings.

The presence of bronchiectasis and liver disease at diagnosis carries a poor prognosis in CVID patients.<sup>7,11</sup> Chronic diarrhea may be present in some patients with CVID.<sup>10,12</sup> Pahari et al had reported a case of recurrent meningitis in a CVID patient.<sup>13</sup> However, in this case, history of chronic diarrhea, meningitis, skin or sinus infection were not found. Besides recurrent infections,

CVID patients have an increased tendency to develop autoimmunity, lympho-proliferative disease and malignancies.<sup>14</sup>

Intravenous immunoglobulin remains the mainstay of therapy in CVID. Prophylactic antimicrobial therapy is another important component of CVID treatment, because immunoglobulin replacement alone may not adequately prevent or treat local and/or persistent infections.<sup>2,6,8</sup> Intravenous antibiotics for a longer duration is recommended for control of acute infective exacerbation of bronchiectasis in CVID patients to prevent relapse. Standard therapy for bronchiectasis like bronchodilators, inhaled corticosteroids, and airway clearance techniques should be optimized for maximum benefit. Newer agents like infliximab or etanercept have been successfully used in a few cases.<sup>7,15</sup>

## CONCLUSION

CVID associated with bronchiectasis is a rare entity. Only early diagnosis and intervention can prevent morbidity and complications of these disorders. PIDs should be suspected if a patient present with recurrent infections and indeed, it is a diagnostic challenge for the attending physicians.

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