

THE CLINICAL SPECTRUM OF RESPIRATORY DISEASES IN PATIENTS WITH PRIMARY ANTIBODY DEFICIENCY

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ABSTRACT

Primary Humoral Immunodeficiencies (PHID) are currently increasingly being recognized. Patients with PHID frequently show respiratory complications.

The objectives of the study is to determine the clinical spectrum of respiratory diseases in patients with PHID.

We extracted data from the clinical files of patients with PHID, diagnosed according to WHO criteria. We encountered 125 patients (84 males), with the diagnosis of primary antibody deficiency including common-variable immunodeficiency (64 pts), x-linked agammaglobulinemia (29 pts), IgA deficiency (20 pts), IgG-subclass deficiency (8 pts), and hyper-IgM syndrome (4 pts). The mean age of the patients at the time of study was 11 years. In the evolution of their disease, 92 cases (73.6%) developed upper respiratory tract infections, among which acute otitis media (68 pts, 54.4%), sinusitis (61 pts, 48.8%), and pharyngitis (12 pts, 10.4%) were found to be the most frequent. Among the lower respiratory tract infections, pneumonia was the most common occurrence (91 pts, 72.8%). The other lower respiratory tract complications were: bronchiectasis (22 pts, 17.6%), bronchitis (8 pts), tuberculosis (6 pts), lung abscess (4 pts), and pneumocystis carinii pneumonia (2 pts).

Respiratory infections constitute the most common presenting symptom of patients with primary humoral immunodeficiency. There may be some differences in the type and frequency of infections in each of these disorders.

Keywords: Primary humoral immunodeficiency, Respiratory infections, Common variable immunodeficiency, X-linked agammaglobulinemia, Selective IgA deficiency, IgG subclass deficiency, Hyper IgM syndrome.

Respiratory Diseases In Immunodeficiency Disorders

INTRODUCTION

Primary immunodeficiencies are now increasingly being recognized, thanks to more knowledge in immunological field and to the availability of more sophisticated diagnostic techniques. Humoral immunodeficiency, being the most frequent primary immune deficiency state, is seen in more than half of the patients⁽¹⁾. These disorders are defined as an abnormal or a decreased quantity and/or function of immunoglobulins, as the products of B-lymphocytes.

This group of disorders is characterized by an exaggerated undue susceptibility to infections, meaning too many, too severe, too prolonged, too complicated, and too unusual infections⁽²⁾. Among the different organs involved, many of the patients present with some kind of respiratory tract infection and these infections constitute the major cause of morbidity and mortality of the patients⁽³⁾. Respiratory tract infections can be subdivided further into two groups of upper respiratory tract infections and lower ones. The upper respiratory tract infections include acute otitis media, sinusitis and pharyngitis, as the most common ones. The lower infections most commonly present as pneumonia, bronchitis, bronchiectasis and lung abscesses.

A wide variety of organisms can cause infections in patients with antibody deficiencies. Among these organisms, encapsulated organisms such as *S. pneumoniae*, and *H. influenza* are very common (1); however, some unusual infections may be seen in some specific disorders. For example, *Pneumocystis carinii* and *Cryptosporidium* infections are seen in Hyper-IgM syndrome (1). Bronchiectasis, as a sequel of delayed diagnosis and late initiation of treatment of these patients, constitutes one of the most challenging complications of such disorders.

Considering the cause of death in these patients, it deserves to note that infections involving the lungs and/or respiratory failure are the most frequent causes of early death when the immune defect is not diagnosed early. Thus, avoidance of pulmonary complications is of special prognostic importance in these patients⁽⁴⁾.

As is obvious, it is necessary for all physicians, especially those encountering the complications of these disorders, to keep in mind the probability of immunodeficiency as the underlying cause of

appearance of such complications and to search for them.

In this study, we reviewed the record of 125 patients with humoral immunodeficiencies, who were referred to our center over a period of 20 years, to provide more detailed characteristics of these disorders and their impact on lung, in particular

PATIENTS AND METHODS

Patients

The Children's Medical Center Hospital is the only referral center for immunodeficient patients throughout the country. Most of the cases, in this center, are from pediatric age group. The diagnosis of humoral immunodeficiencies is based on the standard criteria, published by World Health Organization (WHO) report⁽¹⁾.

Iranian Primary ImmunoDeficiency Registry (IPIDR) is a national registry to enroll patients with the diagnosis of primary immunodeficiencies in Iran. IPIDR is established in the department of immunology, allergy and asthma of this hospital, with a contribution from other universities. In this registry, we have collected the data regarding the patients, family history, past medical history, laboratory tests, and the treatment interventions. Also, this registry has the capabilities of a prospective database, meaning that we can update the patients' records, during their follow-up.

The data, used for this study was extracted from IPIDR.

Statistical Analysis

We performed a descriptive study on our patients. In order to analyze the results, we transferred the data from IPIDR database to Excel 2000 statistical environment, and by using its descriptive capabilities accomplished the task.

The major outcomes, used in this study are respiratory infections including upper respiratory infections and lower ones. These infections include upper respiratory infections, sinusitis, otitis media, pharyngitis, mastoiditis, pneumonia, bronchitis, pulmonary tuberculosis, bronchiectasis, and lung abscess. The attending physician in the hospital documented all of these infections.

RESULTS

In this study, we have analyzed the records of 125 patients with the diagnosis of primary humoral immunodeficiency. These patients were selected from IPIDR during a period of 20 years (1980-2000). They were 84 males and 41 females. Their median age including age range at the time of study is shown (Table 1). These patients have been followed from 1 month to 17 years; on an average, their follow-up period was 5.18 months.

Up to the year 2000, 88 patients were alive, 24 were dead, and 13 could not be traced (Table 2).

Our patient population was further subdivided into 5 subgroups, according to their definitive diagnosis of primary immunodeficiency (Table 1). There were 64 patients with common variable immunodeficiency (CVID), 29 patients with the diagnosis of x-linked agammaglobulinemia (XLA), 20 patients with selective IgA deficiency, 8 patients with selective IgG subclass deficiency, and 4 patients with hyper IgM syndrome (CD40 ligand deficiency).

We have collected all the information regarding different infections, occurring in these patients during the course of their illness. Among the

different organs, involved, respiratory system ranked first. One hundred and twelve patients out of 125 had some form of respiratory system involvement (89.6%). Next to the respiratory system, the gastrointestinal tract involvement occurred in 77 patients, musculoskeletal system in 21 patients, cutaneous infections in 20, and central nervous system involvement in 18 patients.

When we extracted the first manifestation of these patients from their past medical histories, we found that the initial manifestation of immunodeficiency in 86 patients (68.8%) was related to the pulmonary system. Figure 2 shows that in all of the different primary humoral immunodeficiencies, except for hyper IgM syndrome, most of the patients presented with a form of respiratory tract infection as the first manifestation of their disease. Pneumonia was the most frequent presentation, with a frequency of 37.6 percent (47 pts), followed by otitis media (32 pts), and sinusitis. The rest of organs, involved as the first manifestation of primary immunodeficiency were gastrointestinal tract infections, and central nervous system infections. Sepsis was also seen in 3 patients as the primary manifestation.

Table 1. Number of patients with different primary humoral immunodeficiencies (total no=125)

Disease	No. of pts	Male	Female	Median age
X linked agammaglobulinemia	29	29	0	11(5.28)
Common variable immunodeficiency	64	38	26	12(2.42)
Selective IgA deficiency	20	10	10	8.87(325-1758)
IgG subclass deficiency	8	5	3	13.45(7-22.75)
Hyper IgM syndrome	4	2	2	6.5(5.58-11.75)

Table 2. Number of patients with different primary humoral immunodeficiency (n=125)

Disease name	Alive	Dead	Not localizable
X linked agammaglobulinemia	22	4	3
Common variable immunodeficiency	39	17	8
Selective IgA deficiency	16	2	2
IgG subclass deficiency	8	0	0
Hyper IgM syndrome	3	1	0
Total	88	24	13

Respiratory Diseases In Immunodeficiency Disorders

In the evolution of their disease, 92 cases (73.6%) had upper respiratory tract infections, among which acute otitis media (68pts, 54.4%), sinusitis (61 pts, 48.8%), and pharyngitis (13 pts, 10.4%) were found to be the most frequent. Thus one can see that both sinusitis and otitis media occurred in nearly one half of our patients.

Among the lower respiratory tract infections, pneumonia was the most common type of occurrence (91 pts, 72.8%). The other complications included bronchiectasis (22 pts, 17.6%), bronchitis (8 pts), tuberculosis (6 pts), lung abscess (4 pts), and *Pneumocystis carinii* pneumonia (2 pts). Two patients, in whom *Pneumocystis carinii* infection was diagnosed, were among our CVID patients.

DISCUSSION

Primary humoral immunodeficiency constitutes the largest category of immunodeficiency disorders, accounting as much as 50 percent in some reports⁽⁵⁾.

In this broad category, CVID and XLA are the most frequent symptomatic disorders; and together with other humoral disorders such as hyper IgM syndrome, IgG subclass deficiency, symptomatic IgA deficiency, Transient hypogammaglobulinemia of infancy, and functional antibody deficiency will form this broad category. In this study, we studied only the first five diseases.

Such patients, most commonly, present with recurrent bacterial infections, predominantly of the upper and lower respiratory tracts and gastrointestinal tract^(6,7). The major bacteria, involved in all these infections are encapsulated organisms such as *Streptococcus pneumoniae* and *Hemophilus influenza*. *Mycoplasma* is another microbial agent to which CVID patients are particularly susceptible. It is the cause of lung infections in most of the cases. Among the respiratory tract infections, bronchitis, sinusitis and/or otitis media occur in almost all of the CVID patients, as the prototype of primary humoral immunodeficiency^(8,9); however, we found these disorders less frequently. To explain the reason, we can assume that as these upper respiratory tract infections are minor infections, they maybe treated in an ambulatory manner and maybe forgotten to be noted by the parents in the past medical history of the patient. We had found pneumonia in 72.8% of our patients, which is

comparable with other studies^(8,9).

The treatment of choice for these patients is immunoglobulin replacement, either intravenously or intramuscularly. It is shown that the major cause of chronic complications in these patients is a delay in the initiation of specific therapy. Bronchiectasis, as the major complication of chronic lung infection, can lead to major morbidity and mortality for such patients. In our study, the overall frequency of bronchiectasis was 17.6%, which is a little lower than other studies^(8,9).

We also had two cases of *Pneumocystis carinii* pneumonia (PCP). Both of these patients had CVID with very low titers of serum immunoglobulins including IgG, IgM, and IgA. In one of the patients, the IgM was undetectable. This result is somehow different with other studies, which specifically assign PCP to hyper IgM syndrome. None of our 4 patients with the diagnosis of hyper IgM syndrome had *Pneumocystis carinii* infection.

As a conclusion, it is necessary for every physician to keep immunodeficiency in mind in a patient, with recurrent or severe respiratory infection. This task is much more important for respiratory specialists, pediatricians, and internists.

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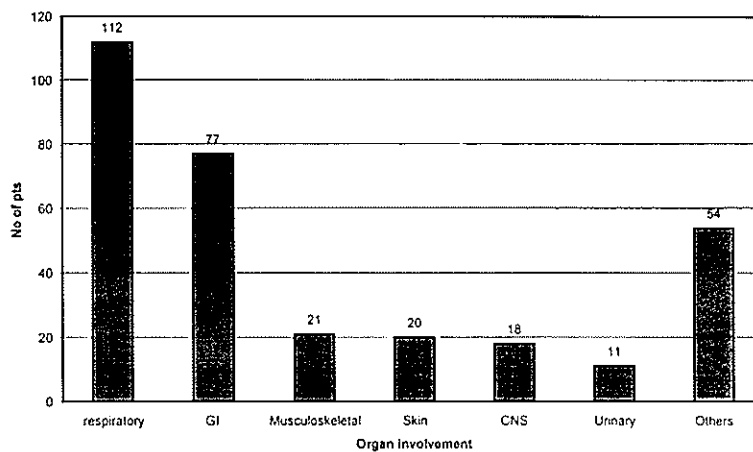


Figure 1. The organ systems, involved in patients with primary humoral immunodeficiency (n=125)

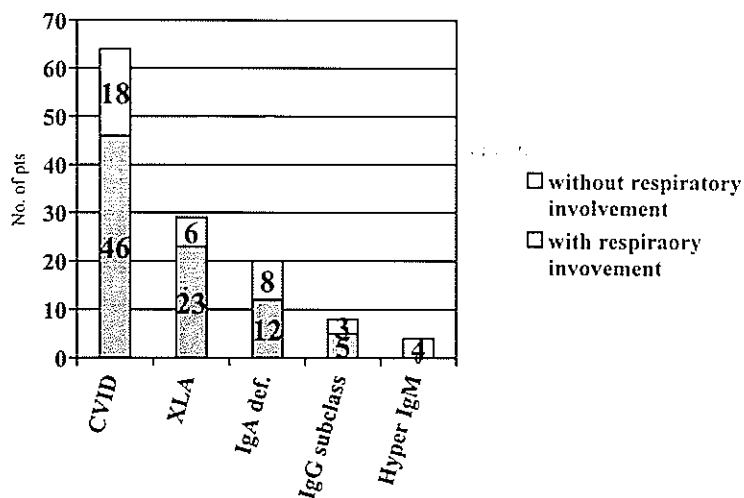


Figure 2. The frequency of respiratory system involvement as the first manifestation of the illness (total number of pts=125)

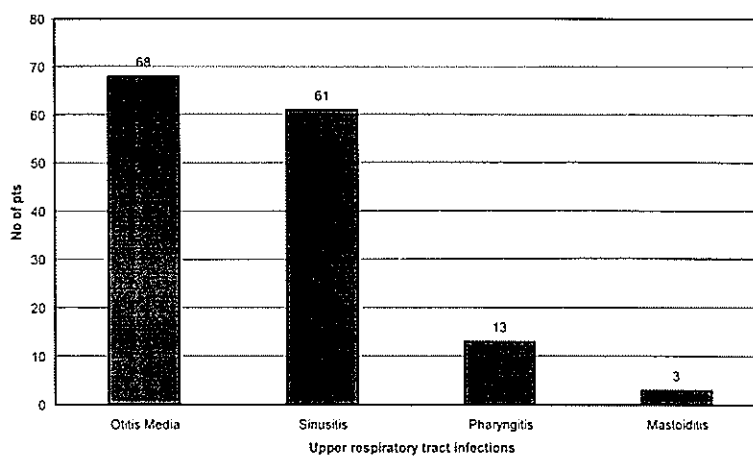


Figure 3. The frequency of upper respiratory tract infections, seen in 92 patients with primary humoral immunodeficiency (total number of pts = 125)

Respiratory Diseases In Immunodeficiency Disorders

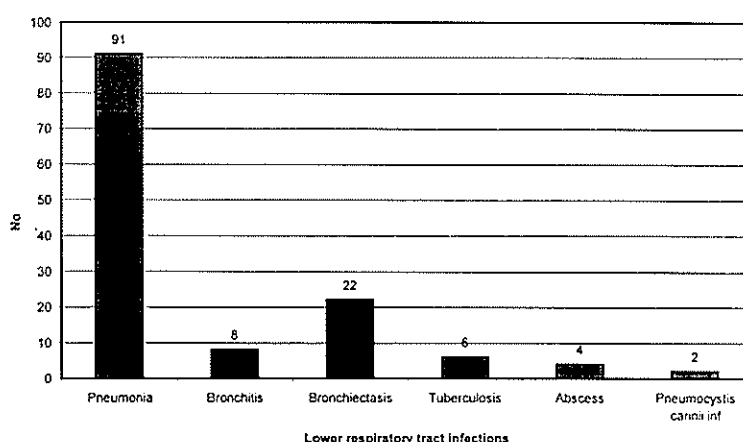


Figure 4. The frequency of lower respiratory tract involvements, seen in patients with diagnosis of primary humoral immunodeficiency (n=125)

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