Medical Journal of the
Islamic Republic of Iran

Volume 16
Number 3
Fall 1381
November 2002

Original Articles

A 20-YEAR SURVEY OF INFECTIOUS COMPLICATIONS IN 64 PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY

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ABSTRACT

Common variable immunodeficiency (CVID) is a heterogeneous primary immunodeficiency disorder, characterized by hypogammaglobulinemia and increased susceptibility to recurrent bacterial infections.

To determine the spectrum of infectious complications in patients with common variable immunodeficiency (CVID), we reviewed the hospital records of 64 CVID patients, who were diagnosed in Children's Medical Center during a period of 20 years.

Among our patients, there were 38 males and 26 females, with a median age of 12 years (2-42 years) at the time of study. The median age of diagnosis was 6.1 years, with an average diagnostic delay of 5.2 years in our patient's group. Almost all of our patients have suffered from acute and recurrent infections, particularly in the respiratory and gastrointestinal systems. The majority of patients (82.5%) had pneumonia prior to diagnosis. The other infectious complications seen in our patients were as follows: recurrent otitis media (54%), recurrent sinusitis (50.8%), diarrhea (65.1%), and bacterial meningitis (11.1%). Unusual or opportunistic infections were also seen in some of our patient population, including oral candidiasis in 10 patients, and *Pneumocystis carinii* pneumonia in 2 subjects.

Based on this study, we suggest that hypogammaglobulinemia should be considered in any patient with a history of recurrent infections in different organs, and such patients should have a full assessment of the immune system.

MJIRI, Vol. 16, No. 3, 123-128, 2002.

Keywords: Common variable immunodeficiency (CVID), Infection, Complication, hypogammaglobulinemia.

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INTRODUCTION

Common variable immunodeficiency (CVID) is a heterogeneous primary immunodeficiency disorder, characterized by hypogammaglobulinemia and increased susceptibility to recurrent bacterial infections.[1] Such bacterial infections constitute most of the morbidity of this disorder. These infections occur most commonly in the sinopulmonary and/or gastrointestinal tract.[2,3] Among the sinopulmonary infections, pneumonia, sinusitis and otitis are more prevalent. On the other hand, chronic lung disease, particularly bronchiectasis, is a common sequel to such infections and cor pulmonale may develop.[2] The major bacteria involved in nearly all of these infections are encapsulated organisms such as *Streptococcus pneumonia*, and *Hemophilus influenza.* Mycoplasma is another microbial agent that these patients are particularly susceptible.

Gastrointestinal infections are particularly common in CVID, especially with organisms such as *Giardia lamblia*, Salmonella, Shigella, and Campylobacter species.

Some patients with CVID present with classic or, more often, atypical inflammatory gastrointestinal disease, resulting in diarrhea, malabsorption, and weight loss.[4]

Along with infections in sinopulmonary and gastrointestinal tracts, these patients are susceptible to some other kinds of infections in other organ systems, which may be the cause of their morbidity or mortality. Among these meningitis, osteomyelitis, septic arthritis, sepsis, and viral infections like disseminated Herpes zoster deserve special attention.[5]

Because of the variability of the symptoms of CVID, physicians in many clinical specialties may visit CVID patients.[4,7] This is probably the reason for a long delay between the onset of disease and the time of diagnosis. Failure to provide adequate therapy during this period will result in tissue and organ damage and several complications for these patients.[5]

The standard treatment for this disorder is regular immunoglobulin replacement, either via intravenous or subcutaneous administration.[6] Several published comparative trials documented the value of higher doses of intravenous immunoglobulin and indicated that infusion of high doses of IVIG is associated with a lower incidence of infections.[8-11]

The purpose of the present study is to determine the spectrum of infectious complications in patients with a definitive diagnosis of CVID, referred to our center over a period of 20 years and to provide more detailed information about infectious complications of this disorder.

MATERIAL AND METHODS

The diagnosis of CVID in our patients has been made according to standard criteria, including reduction of at least two serum immunoglobulin levels (serum IgG, IgA, and IgM) by two standard deviations from normal mean values for age.[1,12]
age, because of a possible diagnosis of transient hypogammaglobulinemia. Also, we have excluded all other causes of hypogammaglobulinemia before making a diagnosis of CVID. For excluding patients with a diagnosis of X-linked agammaglobulinemia, we used patient history, family history of X-linked pattern of inheritance, and immunoflowcytometric values. The data has been gathered from the records of patients, registered in the Iranian Primary Immunodeficiency Registry (IPIDR).

Blood samples of the patients have been tested for immunoglobulin levels on the first visit, using radial immunodiffusion methods. Additionally, antibody deficiency has been confirmed, in many cases, by determining isohemagglutinin titer, and performing Schick test. B and T-cell subset enumeration (CD3, CD4, CD8, and CD19) have been performed in nearly all of our patient's population by using immuno-flowcytometery.

RESULTS

Patients analyzed

From 1980 to 2000, there were 64 patients diagnosed at Children's Medical Center as having CVID. There were 38 males and 26 females. The median age of patients at the time of study was 12 years (2-42 years) (Fig. 1). The median age at the time of disease onset was 9 months (1-408 months) (Fig.2), and at the time of diagnosis was 6.1 years (Fig.3). On average, the diagnostic delay in our patient's group was 5.1 years. By the year 2000, 17 patients had died and 8 patients could not be located. The prevalence of relative marriages was 68.75 percent (in 44 families) among our patients. Also in 21 of these families, a history of recurrent infections in the siblings of the affected patient, with or without a documented diagnosis of immunodeficiency among them was found.

Serum immunoglobulin levels

Considering the lowest levels of immunoglobulins, the

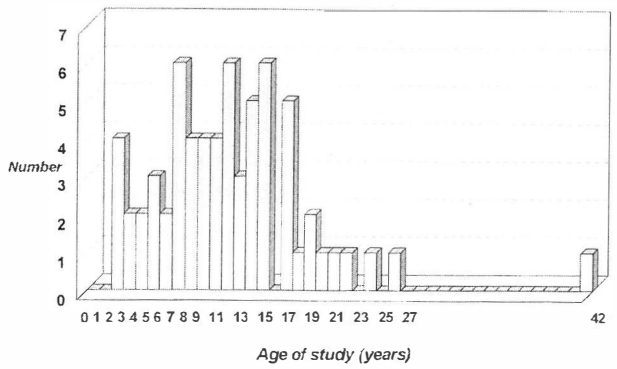

Fig. 1. Age of patients with the diagnosis of common variable immunodeficiency at the time of study (n=64).

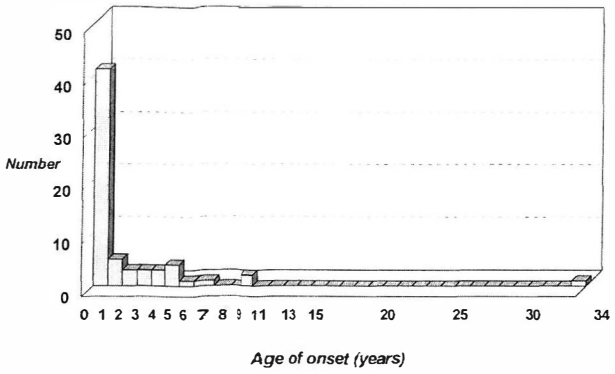

Fig. 2. Beginning age of patients with the diagnosis of common variable immunodeficiency (n=64).

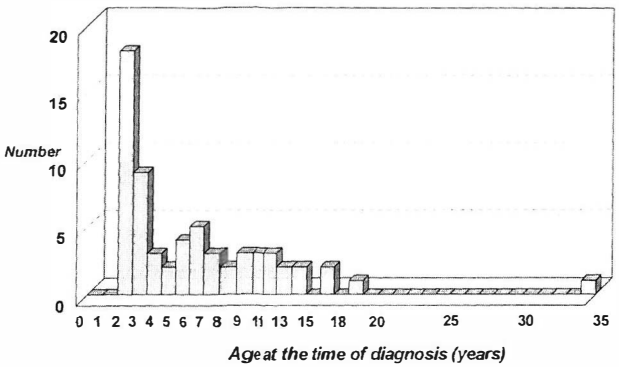

Fig. 3. Diagnosis age of patients with common variable immunodeficiency (n=64).

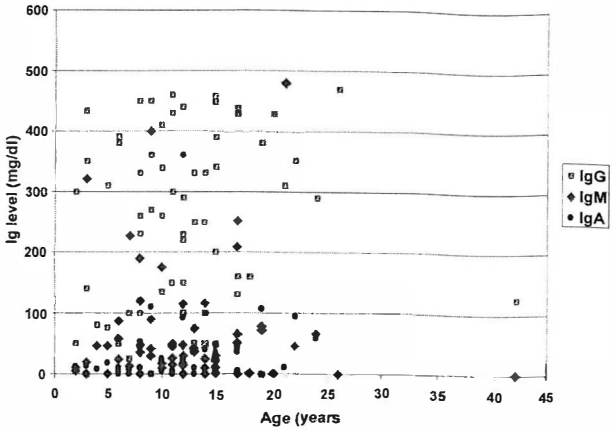

Fig. 4. Serum immunoglobulin levels in patients with common variable immunodeficiency (n=64).

Table I. The spectrum of presenting infections in CVID patients.

	Number of patients	%
Pneumonia	27	38
Otitis	16	23
Diarrhea	13	19
Sinusitis	4	6
Sepsis	3	4
Abscess	3	4
Other infections	4	6

CVID: Common variable immunodeficiency

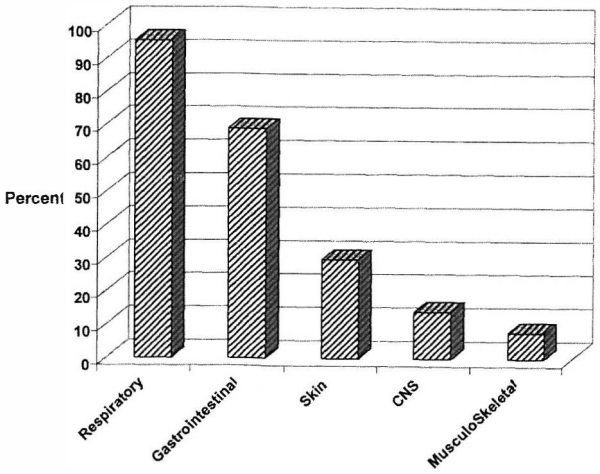

Fig. 5. The prevalence of different organ involvement in patients with common variable immunodeficiency (n=64).

average serum IgG level was 264.1mg/dL, and that of other serum immunoglobulins was 23.4 mg/dL for IgA and 63.4 mg/dL for IgM (Fig. 4). We could not find any difference in serum immunoglobulin levels after adjusting with sex. In some of our patients, T-cell abnormalities were found. T-cell subset analysis, by immuno-flowcytometry, showed that 19 out of 64 (30%) had a reversed CD4/CD8 ratio.

The spectrum of infections as the presenting illness

Forty-seven patients (73.4%) presented with a form of respiratory tract infection as the first manifestation of disease, including pneumonia in 27 patients (42.8%), otitis media in 16 patients (25.4%), and sinusitis in 4 patients (6.3%) (Table I). Other presenting infections included diarrhea in 13 patients (20.6%), sepsis in 3 patients (4.8%), abscess in 3 patients (4.8%), pyelonephritis in 2 patients (3.2%), meningitis in 1 patient (1.6%), and osteomyelitis in 1 patient (1.6%). Also CVID was diagnosed in two of the patients following work-up for lymphadenopathy (Table I).

Infections in the course of disease

Acute and recurrent infections were found in almost all of our patients, particularly involving respiratory and gastrointestinal systems (Fig. 5). Fifty-two out of 64 patients

Table II. Infections associated with CVID and their frequencies of recurrence.

	Number of patients	%
Pneumonia	52	82.5
Acute diarrhea	41	65.1
Acute otitis	34	54.0
Acute sinusitis	32	50.8
Pharyngitis	10	15.9
Candidiasis	10	15.9
Giardiasis	8	12.7
Acute meningitis	7	11.1
Cutaneous abscess	6	9.5
Sepsis	4	6.3
Bronchitis	4	6.3
Conjunctivitis	4	7.9
Septic arthritis	3	4.8
Acute osteomyelitis	3	4.8
Oral ulcer	3	4.8
Pneumocystis carini infections	2	3.2
Mastoiditis	2	3.2
Uveitis	2	3.2
Esophagitis	2	3.2
Disseminated zoster	2	3.2
Acute cystitis	1	1.6
Encephalitis	1	1.6
Meningoencephalitis	1	1.6
Impetigo	1	1.6
Pyoderma	1	1.6
Pericarditis	1	1.6

CVID: Common variable immunodeficiency

(82.5%) had recurrent pneumonia prior to diagnosis, and from these patients, 12 developed bronchiectasis. The diagnosis of bronchiectasis was made according to the patient's history of chronic purulent cough, clubbing of the fingers, x-ray findings, and by excluding chronic bronchitis in them.

Thirty-four of our CVID patients (54%) had a history of recurrent otitis media, and 32 patients (50.8%) had sinusitis.

Recurrent diarrhea was seen in 40 patients (64%). In 10 out of 64 patients (15.9%) unusual or opportunistic infections were seen, including oral candidiasis and *Pneumocystis carinii* pneumonia. Oral candidiasis developed in all of these 10 patients and in 2 of them *P. carinii* pneumonia was found: a 6-month-old infant later found to have CVID, and a 14-year-old boy with severe lack of CD_4 T-cells (less than 300 /mm^2). Prior to initiation of immunoglobulin administration, bacterial meningitis occurred in 7 patients. Other forms of infections and their frequencies were as follows: superficial or deep abscesses in 6 patients, osteomyelitis in 3 patients, septic arthritis in 3 patients and disseminated herpes zoster infection in 2 patients (Table II). The most frequent non-specific symptoms were hepatomegaly in 22 patients, splenomegaly in 20 patients and lymphadenopathy in 16 patients.

DISCUSSION

Common variable immunodeficiency (CVID) is a heterogeneous primary immunodeficiency disorder with variable immunological defects and clinical manifestations. In this study, 64 patients with CVID, referred to our center over a period of 20 years, were evaluated for the presence of infectious complications.

In this group, the median age of patients at the time of study was 12 years, which is somewhat lower than other published studies;[2,4] average age of patients at the time of diagnosis was 31 years (3-79 years). This difference between our patients and Cunningham-Rundles' cases may be due to selection of our patient's population from a pediatric center. However, we do follow our patients through their adulthood and also we have included our adult onset patients.

The median age of our patients at the time of onset of symptoms was 9 months and the median age at the time of diagnosis was 6.1 years. An average diagnostic delay in our patients group was 5.1 years. A survey in the North West Region of England[13] showed that average delay in CVID diagnosis was 2.5 years in children and 5.5 years in adults. Also in a study done by Cunningham-Rundles[4] in USA, the diagnostic delay in 248 studied CVID patients was 4-6 years. All these data show the poor awareness of this condition among general practitioners and pediatricians in our country.

Patients with CVID are more susceptible to recurrent infections and these infections can occur at different organs. In our study 52 out of 64 patients (82.5%) had recurrent penumonia and 12 of them developed bronchiectasis. The same frequency was noted in a study performed by Cunningham-Rundles;[4] and the result of their study showed that 200 out of 248 patients with CVID had at least one episode of pneumonia prior to treatment with immunoglobulin. Also they found that 10 out of 248 patients developed bronchiectasis. It can be concluded that respiratory infections are common medical problems in these groups of patients and failure to provide adequate replacement therapy results in bronchiectasis. Development of bronchiectasis is a serious medical problem[14,15] and all patients with persistent purulent sputum should be assessed and managed, jointly with a chest physician, to prevent progressive lung damage and to monitor functional impairment.[16]

A search for other causes of bronchiectasis is important to exclude their co-existence with antibody deficiency. Despite full replacement immunoglobulin therapy, patients with chronic chest infection always require physiotherapy, antibiotic therapy, bronchodilators and local anti-inflammatory agents if progression of lung damage is to be arrested.

In our study 34 out of 64 patients (54%) had a history of recurrent otitis media and 32 out of 64 patients (50%) had

recurrent sinusitis. It has been shown that immunologic defects have an important role in recurrent ear and sinus infections.[17] A similar study done by Cunningham-Rundles[4] showed that 145 out of 248 patients with CVID (45%) had recurrent sinusitis. Also, some studies have shown that resistant sinus infection can frequently be the first presenting symptom in immune deficiencies especially antibody deficiencies,[18-20] and the infections of the upper respiratory tract (URT) occur several years before the appearance of lower respiratory tract (LRT) infections.[21] Once infections of the LRT are started, the patients have a tendency to neglect URT symptoms.

Patients with recurrent sinusitis should have a full assessment of the immune system. Early detection of antibody deficiency syndromes is of vital importance for prevention of repeated and chronic infections often causing tissue damage in the respiratory tract. Immunoglobulin treatment is essential, but in some patients with late diagnosis, immunoglobulin replacement therapy does not eradicate ENT infections, possibly because of structural damage caused to the mucociliary system. Prolonged use of antibiotics up to 3 months has been demonstrated to improve not only symptomatology but also ciliary function in patients with chronic rhinosinusitis.

In our investigated group, 41 out of 64 (65.1%) had recurrent diarrhea. Recurrent or persistent diarrhea and/or malabsorption may be due to infection, super-infection, food-sensitive enteropathy, autoimmune enteropathy, colitis, ulcerative colitis and celiac disease. Several, careful attempts should be made to detect a pathogen in the stool. Referral to a gastro-enterologist for further investigation and management may be required. Endoscopy may be needed to obtain appropriate biopsies, which should always be stained for specific pathogens (eg. Giardia, Cryptosporidia).

Opportunistic infections including oral candidiasis and *P. carinii* pneumonia were seen in 10 out of 64 of our patients. The isolation of an opportunistic agent in a child or occurrence of an unusually severe infection indicates T- lymphocyte deficiency.[22] Although patients with antibody deficiencies have increased susceptibility to infection by usual organisms such as *S. pneumonia,* and *H. influenza*,[23] but because of T-lymphocyte deficiencies in some cases in this group of patients,[24] some patients with CVID develop opportunistic infections.

According to our data, it is important to consider hypogammaglobulinemia in any patient with a history of recurrent infections at different organ systems;[25] and such patients should have a full assessment of the immune system, including measurement of serum immunoglobulin levels, IgG subclass levels, antibody function evaluation, and B and T-cell subsets enumeration. Serum immunoglobulin levels are interpreted in relation to the normal range for age.[26]

Intravenous or subcutaneous immunoglobulin replacement therapy is the method of choice in patients with common variable immunodeficiency. Adjustment of both dose and infusion interval is empirical and should be based on the patient's clinical state and the preinfusion serum IgG level. The use of symptom diaries by the patient can be an effective way to monitor infections. The diaries can be "personalized" to include details of volumes of sputum produced, number of bowel movements, and antibiotic therapy, and be kept in patient-held records.

CONCLUSION

It is important to consider hypogammaglobulinemia in any patient with a history of recurrent infections at different organ systems, and patients should have a full assessment of the immune system including measurement of serum immunoglobulin levels, IgG subclases, antibody function evaluation and B and T-cell subset enumeration. Serum immunoglobulin levels are interpreted in relation to the normal range for age. Diagnostic delay results in morbidity and complications in untreated patients.

ACKNOWLEDGEMENT

This project could not have been accomplished without the aid and guidance of Dr. Lida Atarod, Dr. Akefeh Ahmadi Afshar, Dr. Nasrin Bazargan and Dr. Arezou Heshmati. We gratefully acknowledge the efforts of Dr. Ali Babaei Jandaghi, Dr. Taha Hojjati Ashrafi, Dr. Jafar Bakhshaie, Dr. Mohsen Nikzad, Dr. Leila Emami, Dr. Mojdeh Vaziri, Dr Laleh Amiri Kordestani, Dr Zohreh Habibi, and Dr. Ali Saghandian Toussi for their role in collecting the data; Also from our medical students of Tehran University of Medical Sciences Including Miss Hengameh Abdollah-pour, Miss Afsaneh Shirani, and Miss Fereshteh Rafiei Samani. We are also grateful to laboratory personnel Mrs. Anna Isaeian, Mrs. Laleh Nikfarjam, Mrs. Anahita Azimdoust and to our secretariat personnel Miss Zahra Shobayri, Miss Nahid Hasani, Miss Helen Eghdami, Mrs. Sholeh Ekrami, and Mrs. Fariba Ghandchi for their arrangements and administrative efforts.

REFERENCES

1- WHO Scientific Committee: Primary immunodeficiency diseases. Report of an IUIS Scientific Committee. International Union of Immunological Societies. Clin Exp Immunol 118 (Suppl 1): 1-28, 1999.

2- Cunningham-Rundles C: Clinical and immunological analysis of 103 patients with common variable immunodeficiency. Journal of Clinical Immunology 9(1): 22-33, 1989.

3- Washington K, Stenzel TT, Buckley RH, Gottfried MR: Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. Am J Surg Pathol 20(10): 1240-52, 1996.

4- Cunningham-Rundles C, Bodian C: Common variable immunodeficiency: Clinical and Immunological features of 248 patients. Journal of Clinical Immunology 92(1): 34-48, 1999.

5- Hermaszewskki RA, Webster ABD: Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. QJ Med 86:31-42, 1993.

6- Chapel H M: Consensus on diagnosis and management of primary antibody deficiencies. Consensus Panel for the Diagnosis and Management of Primary Antibody Deficiencies. BMJ 308(6928): 581-5, 1994.

7- Sneller MC, et al: NIH Conference. New insights into common variable immunodeficiency. Ann Intern Med 118(9): 720-30, 1993.

8- Cunningham-Rundles C, Siegal FP, Smithwick EM, et al: Efficacy of intravenous immunoglobulin in primary humoral immunodeficiency disease. Ann Intern Med 101(4): 345-9, 1984.

9- Ochs HD, Fischer SH, Wedgwood RJ, et al: Comparison of high-dose and low-dose intravenous immunoglobulin therapy in patients with primary immunodeficiency diseases. Am J Med 76(3A): 78-82, 1984.

10- Roifman CM, Levison H, Gelfand EW: High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. Lancet 1 (8541): 1075-7, 1987.

11- Mushiake K, Motoyoshi F, Kondo N, et al: Long-term follow up of patients with common variable immunodeficiency treated with intravenous immunoglobulin: reevaluation of intravenous immunoglobulin replacement therapy. IVIG therapy in CVID. Biotherapy 7(2): 101-7, 1993-94.

12- 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 93(3):190-7, 1999.

13- Blore J, Haeney M: Primary antibody deficiency and diagnostic delay. BMJ 298: 516-7, 1989.

14-. Newson T, Chippindale AJ,Canr AJ: Computed tomography scan assessment of lung disease in primary immunodeficiencies. Eur J Pediatr 158 (1): 29-31, 1999.

15- Kainulainen L, Varpula M, Liippo K, Svedstrom E, Nikoskelainen J, Ruuskanen O: Pulmonary abnormalities in patients with primary hypogammaglobulinemia. J Allergy Clin Immunol 104(5): 1031-6, 1999.

16- Bjorkander J, Blake B, Hanson LA: Primary hypogammaglobulinaemia: impaired lung function and body growth with delayed diagnosis and inadequate treatment. Eur J Respir Dis 65: 529-36, 1984.

17- Sethi DS, Winkelstein JA, Lederman H, Loury MC: Immunologic defects in patients with chronic recurrent sinusitis: diagnosis and management. Otolaryngol Head Neck Surg 112(2): 242-7, 1995.

18-Armenaka M, Grizzanti J, Rosenstreich DL: Serum immunoglobulins and IgG subclass levels in adults with chronic sinusitis: evidence for decreased IgG_3 levels.Ann Allergy 72(6): 507-14, 1994.

19-May A, Zielen S, von Ilberg C, Weber A: Immunoglobulin deficiency and determination of pneumococcal antibody titers in patients with therapy-refractory recurrent rhinosinusitis. Eur Arch Otorhinolaryngol 256(9):445-9, 1999.

20-Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman C W: Immunologic defects in patients with refractory sinusitis. Pediatrics 87(3): 311-6, 1991.

21-Karlsson G, Petruson B, Bjorkander J, Hanson LA: Infections of the nose and paranasal sinuses in adult patients with immunodeficiency. Arch Otolaryngol 111(5): 290-3, 1985.

22. Aghamohammadi A, Strobel S, Novelli V, Holzel H, Morgan JA single center retrospective 5 year survey of infectious complications in 85 children with combined immunodeficiency. Acta Medica Iranica 34(1,2): 7-13, 1996.

23-Stiehm E R, Chin T W, Hass A, et al: Infectious complications of primary immunodeficiencies. Clin Immunol Immunopathol 40: 69-86, 1986.

24-Fisher M, Hauber J, Eggenbauer H, et al: A defect in early phase of T-cell receptor mediated T-cell activation in patients with common variable immunodeficiency. Blood 84: 4234-4241, 1994.

25- Dizon J G, Goldberg B J, Kaplan M S: How to evaluate suspected immunodeficiency. Pediatr Ann 227(11): 743-50, 1998.

26-Pacheco S E, Shearer W T: Laboratory aspects of immunology. Pediatric Clinics of North America 41(4): 623-655, 1994.