Neutropenia in Patients with Primary Antibody Deficiency Disorders

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ABSTRACT

Neutropenia is characterized by decrease in the absolute number of circulating neutrophils and an increase susceptibility to infections. The current study was performed in order to explain the clinical and laboratory findings of patients with antibody deficiency disorders associated neutropenia.

The patients' records of 19 neutropenic cases out of 207 patients with antibody deficiencies, who had been referred to Children's Medical Center and enrolled in Iranian primary immunodeficiency registry, were reviewed.

Nineteen cases (14 male and 5 female), with a mean age of 10.7±5.7 years, were associated with neutropenia (9.2%). The disorders with associated neutropenia were Hyper IgM syndromes (3 of 8), Common variable immunodeficiency (13 of 109), and X-linked agammaglobulinemia (3 of 45). The median age for the onset of disease and diagnosis age were 15 months (1-134) and 3.8 years (6 months-13 years), respectively. The most common infections during the course of illness were pneumonia (13 cases), diarrhea (12 cases), oral candidiasis (9 cases), otitis media (6 cases), sinusitis (6 cases), cutaneous infections (5 cases), and abscess (5 cases). Other less frequent infections were: conjunctivitis, oral ulcers, meningitis, and osteomyelitis. Three neutropenic patients died because of recurrent infections.

Neutropenia may occur in any of the primary immunodeficiency disorders. Persistent or severe infections always pose a supposition, which deserves further evaluation for detecting an underlying immune deficiency syndrome and neutropenia, since a delay in diagnosis may result in a serious organ damage or even death of the patient.

Keywords: Neutropenia, Immunologic Deficiency Syndromes, Infection, Iran

INTRODUCTION

Primary immunodeficiency syndromes are relatively rare disorders, characterized by an unusual susceptibility to infections.[1,2] Some conditions with primary immunodeficiencies may also feature neutropenia as a consequence of either an intercurrent infection or an autoimmune disease.[3,4] Neutropenia is a reduction in the absolute neutrophil count to less than 1500/mm^3.[5,6] Impaired production, peripheral destruction, and abnormal distribution of neutrophils may lead to low number of circulating granulocytes.[7] The clinical

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presentation may be: fever of unknown origin, gingivitis, stomatitis, oral ulcers, cellulitis, perirectal abscess or more severe systemic pyogenic infections.[8] The present study reports the clinical and laboratory findings of Iranian patients with antibody deficiencies associated neutropenia from Children's Medical Center.

MATERIALS AND METHODS

Two hundred and seven patients with the diagnosis of antibody deficiency disorders have so far been referred to Iranian Primary Immunodeficiency Registry (IPIDR).[2] All of these patients have been diagnosed based on the standard criteria for primary immunodeficiency disorders.[1] Nineteen of them had associated neutropenia. These patients have been referred to Children's Medical Center and followed-up for at least one year and neutropenia has been detected with at least 2 repeated tests in a period of 3 months. In order to determine the clinical and laboratory findings of hypogammaglobulinemia patients with neutropenia, their medical documents during a 24-year period (1980-2004) were reviewed in a retrospective study.

Neutropenia is defined as a significant reduction in the absolute neutrophil count (ANC) of circulating neutrophils in the blood, which is calculated by multiplying the total of blood cell count by the percentage of neutrophils plus bands noted in the differential cell count.[6]

Neutropenia has been subclassified to: mild, moderate or severe, based on the ANC: mild, 1000 to 1500/mm^3; moderate, 500 to 1000/mm^3; and severe, less than 500/mm^3.[5,6] The definition of the leukopenic pattern is a decreased number of white blood cells (<4000/mm^3).[8]

In order to determine the frequency and duration of infections, a review of the clinical history was performed. Data analysis was performed using SPSS statistical software package, version 10.0 (SPSS Inc, Chicago, IL).

RESULTS

Characteristics of Patients

Nineteen cases (14 male and 5 female) out of 207 antibody deficient patients were associated with neutropenia (9.2%). The disorders with associated neutropenia were hyper IgM syndromes (HIgM), common variable immunodeficiency (CVID), and X-linked agammaglobulinemia (XLA) (Table 1). The mean age of these patients with neutropenia was 9.6 ± 6.6 years (range: 2-22 years), and were followed through a period of 6.8 ± 4.6 years. The median age for the onset of disease was 15 months (1-134). Among these patients: 31.6% experienced symptoms by the age of 1 month, and 89.5% by the age of 2 years. The median age at the time of primary immunodeficiencies diagnosis was 3.8 years (6 months-13 years), with a median diagnosis delay of 22 months (<1 month - 12 years) (Table 2). Twelve of these patients are alive, 4 patients could not be traced since one year ago, and the remaining 3 patients died because of recurrent infections.

Laboratory Findings

Laboratory analysis revealed that median serum levels of IgG, IgM, and IgA were 200, 10, and 5 mg/dl, respectively. ANC was low in these patients, with the mean count of 787.9 ± 435.9 cells/mm^3 (range: 25-1368/mm^3), at the time of diagnosis. Also, the median count of white blood cells and monocytes were: 3600/mm^3 (range: 1880-9600/mm^3) and 119.6/mm^3 (range: 25-945/mm^3), respectively. According to the classification of neutropenia, 6 patients suffered from severe, 8 moderate, and 5 mild neutropenia, respectively (Table 3).

Table 1. Frequency of neutropenia in primary antibody deficiency disorders.

Name of disease	Registered patients (n=474)		Patients with neutropenia (n=56)		Incidence of neutropenia in each disease
	Number	Percent	Number	Percent	
X-linked agammaglobulinemia	45	9.49	3	5.36	6.67%
Hyper IgM syndromes	8	1.69	3	5.36	37.5%
Common variable immunodeficiency	109	22.99	13	23.21	11.93%
Selective IgA deficiency	35	7.38	0	0	0%
IgG subclass deficiency	10	2.11	0	0	0%

Table 2. Onset age and diagnosis age of neutropenic patients with antibody deficiency disorders.

Primary antibody deficiency disorders	Current age (years)		Onset age (months)		Diagnosis age (months)		Diagnosis lag (months)	
	Median	Range	Median	Range	Median	Range	Median	Range
X-linked agammaglobulinemia	12	3-15	4	1-11	29	11-47	25	0-46
Hyper IgM syndromes	7	4-9	1	1-24	48	24-48	47	0-47
Common variable immunodeficiency	5	2-22	10	1-34	31	6-156	20	1-144

Presenting Illness

The most common presenting complaints were diarrhea in 6 cases, pneumonia in 3 cases, otitis media in 3 cases, and cutaneous infections in 3 cases. The other presenting manifestations were sinusitis, pyelonephritis, and lymphadenitis.

In one patient the diagnosis of primary immunodeficiency syndrome was made after follow-up of hepatosplenomagaly.

Infections during the Course of Disease

The most common infections during the course of illness were respiratory infections, which were seen in 17 patients (89.5%). The most commonly occurred manifestations (in descending order of frequency) were: pneumonia (13 cases), acute diarrhea (12 cases), oral candidiasis (9 cases), otitis media (6 cases), sinusitis (6 cases), cutaneous infections (5 cases), and abscess (5 cases). Abscesses have been detected in perianal, cutaneous, submandibular, and peritonsillar regions. Other less frequent infections were: conjunctivitis (2 cases), oral ulcers (2 cases), meningitis (1 case), and osteomyelitis (1 case) (Table 4). Also, 3 cases with failure to thrive were noticed among these patients. Non-specific symptoms like hepatomegaly and splenomegaly were already seen in 47.4% and 42.1% of the patients, respectively. Also, 11 of these patients were associated with leukopenia (57.9%), 11 had anemia (57.9%), and 7 thrombocytopenia (36.8%).

DISCUSSION

Neutropenia is mostly characterized by decrease in neutrophils and an increase in susceptibility to infections.[9] The present study describes the clinical and laboratory findings of antibody deficient patients, who were associated with neutropenia. Neutropenia in our patients was reported to be severe in 6, moderate in 8, and mild in 5 patients respectively. As was seen in our study, neutropenia and leukopenia occurred together, in most situations.[7] Neutropenia may occur in any of the primary immunodeficiency disorders as a consequence of either an intercurrent infection or an autoimmune disease.[3,4] More than one-third of our HIgM experienced neutropenia.

Table 3. Laboratory findings of neutropenic patients with antibody deficiency disorders.

Primary antibody deficiency disorders	White blood cells	Absolute neutrophil count	Neutropenia*			Leukopenia*	Anemia*	Thrombocytopenia*
	Median (range)	Median (range)	Severe	Moderate	Mild			
X-linked agammaglobulinemia	3600 (2400-7200)	1368 (696-1368)	-	1	2	1	2	1
Hyper IgM syndromes	4500 (4400-4800)	768 (200-864)	1	2	-	1	3	2
Common variable immunodeficiency	2600 (1880-9600)	910 (25-1324)	5	5	3	9	6	4

* Number of patients

Table 4. Infections during the course of disease in neutropenic patients with antibody deficiency disorders.

Primary antibody deficiency disorders	Number of patients with infections (percent in each disorder)										
	Pneumonia	Otitis Media	Acute diarrhea	Abscess	Oral Candidiasis	Oral Ulcer	Cutaneous infection	Sinusitis	Conjunctivitis	Meningitis	Osteomyelitis
X-linked agammaglobulinemia	2 (66.7)	3 (100)	1 (33.3)	-	-	-	-	2 (66.7)	-	-	-
Hyper IgM syndromes	1 (33.3)	-	2 (66.7)	2 (66.7)	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)	-	-
Common variable immunodeficiency	10 (76.9)	3 (23.1)	9 (69.2)	3 (23.1)	7 (53.8)	1 (7.7)	4 (30.8)	3 (23.1)	1 (7.7)	1 (7.7)	1 (7.7)

The high incidence of neutropenia had been reported previously by the European Society for Immunodeficiency, out of which 68% out of 56 HIgM patients were reported as having neutropenia.[10] Although the etiology of their neutropenia was unclear, an autoimmune basis could be suggested, as there were other manifestations of autoimmunity in these patients.[3,11] Also the neutropenia in our patients with CVID may occur on an autoimmune basis.[3] It seems that the autoimmune neutropenia is a common cause of neutropenia in some primary specific immunodeficiencies.[9] Approximately 7% of our XLA had neutropenia. According to the first report of XLA in Iran, hematological abnormalities were uncommon. Transient neutropenia was seen in one case and transient thrombocytopenia occurred in another patient, and both of these abnormalities occurred in association with acute infections.[12] However neutropenia has been reported in a significant proportion of patients with XLA, an association which could be explained by this fact that the XLA gene is expressed in cells of myeloid lineage.[3] Intermittent neutropenia, which is often manifested at the beginning of an infection[13], may be reflective of Bruton's tyrosine kinase (Btk). Btk is the only one of several signaling molecules participating in myeloid maturation and neutropenia would be observed in XLA only when rapid production of such cells is needed.[14]

An increased susceptibility to infections was noticed in our patients. Respiratory infections were the most common type of involvement in these patients. Approximately one third of the patients presented with upper and lower respiratory tract infections at the first visit and 86% of them had at least one of the respiratory involvements during their illness. Also a highly increased incidence of gastrointestinal involvement and oral manifestations were noticed as the first manifestations during their disease.[6] For patients presenting with unexpected neutropenia, the clinical history and examination of the peripheral blood smears were most important part of the diagnostic evaluation. Examination of the oral cavity, perianal region, and skin is necessary in order to assess the clinical impact of chronic neutropenia. The presence of gingivitis, ulcer, and abscess implies clinically significant neutropenia.[5] Recurrent infections are the hallmark of significant neutropenia. Neutropenia could aggravate the complications of patients with antibody deficiency disorders. Common sites of infection include the oral cavity and mucous membranes. The skin is an important sentinel site for infection with rash, ulcerations, and abscesses. Perirectal and genital areas are also susceptible to repeated infections.[5,6] Therefore, patient's quality of life and life expectancy will be good through the help of attentive physicians and dentists.[15]

The diagnosis of the various types of neutropenia rests primarily on the clinical picture and family studies (if indicated); since these disorders share similar blood and bone marrow pictures. Review of the clinical history is important to rule out drug exposure and underlying illnesses such as auto-immune diseases, and in order to determine the frequency and duration of infections. Bone marrow examination (in order to exclude an infiltrative

process) may be necessary, especially in adults, if the clinical history is noncontributory.[7] Children or adults presenting with repeated infection and neutropenia should be evaluated for antibody deficiency, with laboratory investigations tailored to the type of infections experienced.[3] Unusual, persistent or severe infections must always initiate the search for an antibody deficiency disorders, because a delay in diagnosis may result in chronic infection, irretrievable end-organ damage or even death of the patient.[11] The spectrum of assays offered by laboratories will need to be increased as defects of this type become recognized. Timely referral to a clinical immunologist remains the key to the successful diagnosis and management of patients with antibody deficiency.[16] It could open new possibilities for understanding the physiological and pathological processes more precisely, and offers new opportunities to treat these conditions and to use the new knowledge to develop therapies in which the phagocytic system participates.[17] Additional research into the genetic causes of these disorders is likely to shed further light on myelopoiesis and the mechanisms of neutropenia.[3]

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