

# Clinical and Laboratory Findings in Iranian Children with Cyclic Neutropenia

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## ABSTRACT

Cyclic neutropenia is a rare immunodeficiency syndrome, characterized by regular periodic oscillations in the circulating neutrophil count from normal to neutropenic levels through 3 weeks period, and lasting for 3-6 days. In order to determine the clinical features of cyclic neutropenia, this study was performed.

Seven patients with cyclic neutropenia (3 males and 4 females), who experienced neutropenic periods every 3 weeks (5 with severe and 2 with moderate neutropenia), were investigated in this study. They had been referred to Iranian Primary Immunodeficiency Registry during 23 years (1980-2003).

The range of patients' ages was from 7 to 13 years (median 11 years). The median age at the onset of the disease was 12 months (1 month- 2 years) and the median age of diagnosis was 2 (1.5-5) years, with a median diagnosis delay of 1 year (2 months- 5 years). Neutropenia was associated with leukopenia (3 patients), anemia (3 patients), and thrombocytopenia (1 patient). Patients were asymptomatic in healthy phase, but during the episode of neutropenia suffered from aphthous ulcers, abscesses and overwhelming infections. The most commonly occurred manifestations were: otitis media (6 cases), oral ulcers (5 cases), abscesses (4 cases), pneumonia (3 cases), diarrhea (3 cases), oral candidiasis (3 cases), cutaneous infections (2 cases), and periodontitis (2 cases). One of these patients subsequently died because of recurrent infections.

Unusual, persistent or severe infections should be the initiating factors to search for an immune deficiency syndrome such as cyclic neutropenia, because a delay in diagnosis may result in chronic infection, irretrievable end-organ damage or even death of the patient.

**Keywords:** Immunologic Deficiency Syndromes, Infection, Iran, Neutropenia.

## INTRODUCTION

Cyclic neutropenia is an autosomal dominant disease,

characterized by neutropenia occurring every 3 weeks lasting for 3-6 days. It is a rare primary immunodeficiency disorder which the phagocytic system is involved.<sup>1,2</sup> The phagocytic system is an essential part of the host immune defence and is the main component of the innate immune system. Clinically, defects in this system can lead to specific symptoms such as recurrent cutaneous abscesses, periodontitis, and aphthous ulcers.<sup>1</sup> The most commonly encountered phagocytic

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defect is a decrease in the absolute number of circulating neutrophils.<sup>3</sup> Although neutropenia may occur in any of the primary immunodeficiency disorders<sup>4</sup> congenital neutropenia may be seen only in some of these disorders such as cyclic neutropenia.<sup>5-8</sup> The original case of cyclic neutropenia, reported by Leale in 1910, was an infant with repeated episodes of fever, stomatitis, skin infections, and neutropenia.<sup>9</sup> Subsequently, more than 100 patients with a similar disorder have been reported.<sup>6</sup>

Patients with cyclic neutropenia are usually asymptomatic, but during the episode of neutropenia suffer from fever of unknown origin, gingivitis, stomatitis, aphthous ulcers, cellulitis, perirectal abscess and more severe systemic pyogenic infections.<sup>1,7</sup>

The present study reports the clinical and laboratory findings of patients with cyclic neutropenia from Children's Medical Center, one of the immunodeficiency referral centers in Iran, where Iranian Primary Immunodeficiency Registry (IPIDR) is founded.<sup>10</sup>

**PATIENTS AND METHODS**

In order to determine the clinical and laboratory findings of cyclic neutropenia in Iranian patients with primary immunodeficiency, the records of 7 patients, who had been referred to Children's Medical Center Hospital, were reviewed. These data have been gathered by interviewing the patients and reviewing their medical documents during a 23- year period (1980-2003).

Cyclic neutropenia is described by regular periodic oscillations in the circulating neutrophil count from normal to neutropenic levels through 3 weeks period, lasting for 3-6 days.<sup>1,2,8</sup> Diagnosis of our patients was based on the findings of characteristic recurrent infections with cyclic neutropenia.<sup>6</sup>

Neutropenia is defined in our study 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.<sup>6</sup> Neutropenia has been sub classified to: mild, moderate or severe, based on the ANC: mild, 1000 to 1500/mm<sup>3</sup>; moderate, 500 to 1000/mm<sup>3</sup>; and severe, less than 500/mm<sup>3</sup>.<sup>5,6</sup> The definition of the leukopenic pattern is a decreased number of white blood cells (<4000/mm<sup>3</sup>).<sup>8</sup> Because the cycling periodicity might vary from patient to patient, twice weekly blood samples were obtained for 4 weeks when seeking to document cyclic neutropenia.<sup>6</sup>

Data analysis was performed using SPSS statistical software package, version 10.0 (SPSS Inc, Chicago, IL).

**RESULTS**

Seven patients with cyclic neutropenia (3 males and 4 females) were reviewed and followed through a median period of 4 years (1-10 years). The median age of patients at the time of study was 11 years (range: 7-13 years) and the median age for the onset of disease was 12 months (1 month - 2 years). The median age at the time of diagnosis was 24 months (1.5-5 years), with a median diagnosis delay of 12 months (2 months - 5 years) (Table 1).

Two out of 7 patients had a positive familial history of recurrent infections suggesting the possible existence of primary immunodeficiency disorders in their families.

The most common presenting complaint in these patients had been oral ulcer, seen in 3 patients (42.8%). The other presenting manifestations were: otitis (2 patients), pneumonia (1 patients), and cutaneous abscess (1 patient).

Patients were asymptomatic in the healthy phase, but during the episode of neutropenia suffered from aphthous ulcers, abscesses and overwhelming infec-

**Table 1.** Characteristics of patients with cyclic neutropenia.

Patient	Sex	Birth Place	Age (years)	Age of onset (months)	Age of diagnosis (months)	Follow up period (years)	White Blood Cell*	Absolute Neutrophil Count*
P1	Female	Tehran	13	1	36	10	4900	490
P2	Female	Tehran	12	24	30	2	2000	200
P3	Male	Karaj	12	16	18	5	2500	250
P4	Male	Tehran	11	1	60	6	4900	343
P5	Male	Tehran	8	12	24	5	2200	220
P6	Female	Mian Doab	7	12	24	2	7500	900
P7	Female	Mahmoud Abad	8	4	24	4	6700	871

\*At the time of diagnosis.

tions. During the course of illness, all of the patients developed respiratory infections, and 85% had concomitant oral manifestations. The most commonly occurring manifestations (in descending order of frequency) were: otitis media (6 cases), oral ulcers (5 cases), abscess (4 cases), pneumonia (3 cases), diarrhea (3 cases), oral candidiasis (3 cases), cutaneous infections (2 cases), and periodontitis (2 cases). One of these patients subsequently died because of recurrent infections. Failure to thrive, hepatomegaly, and splenomegaly were also detected in 1, 2, and 1 cases, respectively. Four patients suffered from abscesses in different organs including: skin, perianal, mastoidal, submandibular, peritonsillar, and lung.

Six out of these patients are alive, and 1 patient died because of recurrent infections (P1 in 2002). They were followed-up for a period of 2 to 10 years.

Laboratory analysis revealed that ANC was low in these patients, with a mean count of  $467.7 \pm 301.7$  cells/mm<sup>3</sup> (range: 200-900/mm<sup>3</sup>), at the time of diagnosis (Table 1). Also, the median count of white blood cells and monocytes were: 4900/mm<sup>3</sup> (range: 2000-7500/mm<sup>3</sup>) and 577/mm<sup>3</sup> (range: 75-1127/mm<sup>3</sup>), respectively. According to the classification of neutropenia, 5 patients suffered from severe and 2 from moderate neutropenia, at the time of diagnosis. Also, 3 out of these patients showed leukopenia (42.9%), 3 had anemia, and 1 had thrombocytopenia, and only two patients had monocytosis (P1 and P7).

Bone marrow examination was accomplished in two patients during the neutropenic period. The myeloid population composed predominantly of myelocytes and a minor number of promyelocytes and metamyelocytes. The myelocytic maturation arrest was seen in both patients.

## DISCUSSION

Cyclic neutropenia is a hematological disorder and rare primary immunodeficiency disorder consisting of the periodic failure in production of granulocytes, presumably at the stem cell level. The symptomatic episodes of fever and mild infections usually recur approximately every 3-4 weeks. The neutropenic periods, lasting 3-6 days, are associated with infections of mucosal sites such as oral, upper respiratory tract or rectal regions.<sup>2,6,8</sup> The present study describes the clinical and laboratory findings of 7 patients with cyclic neutropenia from IPIDR.

All of our patients were in pediatric group, which is in agreement with this statement that this characteristic clinical syndrome usually presents in infancy or childhood.<sup>6</sup>

An increased susceptibility to infections was de-

tected in our patients. Respiratory infections and oral manifestations were the most common type of involvement in these patients. Approximately half of the patients presented with upper and lower respiratory tract involvement at the first visit and all of them had at least one of the respiratory involvements during their illness. Also, a highly increased incidence of oral manifestations was noticed as the first manifestation (42%) and during their disease (85%). For patients presenting with unexpected neutropenia. The clinical history and examination of the peripheral blood smear are important aspects of the diagnostic evaluation. Examination of the oral cavity, perianal region, and skin is necessary in order to assess the clinical impact of neutropenia. The presence of gingivitis, ulcer, and abscess implies clinically significant neutropenia.<sup>5</sup> Recurrent infections are the hallmark of significant neutropenia. Common sites of infection include the oral cavity and mucous membranes, where mouth ulcers and periodontitis are common. The skin is a second sentinel site of infection with rash, ulcerations, and abscesses. Perirectal and genital areas are also susceptible to repeated infections.<sup>5,6</sup> During periods of neutropenia, our patients experienced repeated episodes of otitis media, oral ulcers, pneumonia, abscesses and acute diarrhea. Recurrent infections with a periodicity of about 3 weeks should alert the physicians to the possibility of cyclic neutropenia. Although cyclic neutropenia is characterized by severe neutropenia at 21-day intervals,<sup>1</sup> two out of our 7 patients suffered moderate neutropenia. Neutropenia was associated with leukopenia, anemia, and thrombocytopenia in some of our patients. Neutropenia and leukopenia occur together, in most situations.<sup>8</sup> It seems that these are associated with cyclical variations in blood-cells production.<sup>1,2</sup> The bone marrow of our 2 investigated patients showed maturation arrest during neutropenic period. Bone marrow studies demonstrate absence of granulocytes and granulocyte precursors or a maturation arrest before the onset of peripheral neutropenia.<sup>1,6</sup> The exact cause of cyclic neutropenia is unknown. It could be suggested that cyclic neutropenia is due to an abnormality in the regulation of early hematopoietic precursor cells. With the help of attentive physicians and dentists, patient's quality of life and life expectancy are good.<sup>9</sup>

Unusual, persistent or severe infections should be carefully investigated to eliminate the possibility of cyclic neutropenia, because a delay in diagnosis might result in chronic infection, irretrievable end-organ damage or even death of the patient.<sup>11</sup> The spectrum of assays offered by laboratories will need to be increased as defects of this type becomes recognized. Timely referral to a clinical immunologist remains the key to the successful diagnosis and management of patients with

immunodeficiency.<sup>12</sup> It could open new possibilities for understanding the physiological and pathological processes more precisely, and offer new opportunities to treat these conditions and to use the new knowledge to develop therapies in which the phagocytic system participates.<sup>1</sup>

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