A Single Center Survey of Patients With Congenital Neutropenia: Report From Northwestern Iran

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Abstract- Neutropenia is characterized by a decrease in circulating neutrophil counts and consequent infections. The present study was performed to describe the clinical and laboratory findings of patients with congenital neutropenia in northwestern Iran. Medical records of 31 patients with congenital neutropenia out of 280 neutropenic patients who had been referred to Tabriz Children's Hospital during a 3-year-period (2011-2014), were reviewed. Thirty-one cases (17 female and 14 male), with a mean age of 46.21±37.92 months, were diagnosed to suffer from congenital neutropenia. The disorders associated with congenital neutropenia were combined immunodeficiency (8 cases), severe congenital neutropenia (6 cases), common variable immunodeficiency (4 cases), severe combined immunodeficiency (2 cases), and metabolic syndrome (1 case). The median age of the onset of disease was 13.16±12.48 months. The most common clinical manifestations during the course of illness were otitis media (13 cases), pneumonia (12 cases), recurrent aphthous stomatitis, lymphadenopathy, and gingivitis (11 cases). Four neutropenic patients died because of recurrent infections. Neutropenia may occur in the context of the primary immunodeficiency disorders. Unusual, persistent or severe infections always pose a speculation to search for an underlying immunodeficiency syndrome and neutropenia, so as to avoid further life-threatening complications as a result of any delay in diagnosis.

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Introduction

Neutropenia refers to a decrease in circulating neutrophil counts in the peripheral blood. Neutrophils are known as the most abundant type of white blood cell and are the first line of the innate immunity against infection. The major cause of morbidity and mortality in neutropenic patients is infection, which could progress rapidly resulting in serious complications (1). The risk of life-threatening complications depends mainly on the duration of neutropenia (1), and this could explain the clinical importance of timely diagnosis of this condition. The causes of neutropenia could be categorized into four major groups, including those leading to decreased production, ineffective production (defect in neutrophils transfer from the bone marrow to the peripheral blood), increased sequestration and margination, or increased destruction of neutrophils. Neutropenia may be classified as acute or chronic (lasting longer than six months) and acquired or congenital (2). The acquired neutropenia, which is attributed to the shortening of neutrophils lifespan due to enhanced consumption or destruction of these cell types in the peripheral blood, leads to a substantially lower risk of development of infections,

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compared to congenital neutropenia (3). The acquired neutropenia encompasses a wide range of etiologies, comprising infection-induced neutropenias, pregnancy or delivery-related neutropenias, alloimmune neonatal neutropenia, neonatal alloimmune neutropenia secondary to maternal autoimmune neutropenia, secondary autoimmune neutropenias, medication-induced neutropenias, autoimmune neutropenia associated with neoplasms, and vitamin B12, folate or copper deficiency (4). On the other hand, congenital neutropenias, which develop as a result of disruption in different stages of neutrophils' growth or maturation process, occur rarely; however, this entity is clinically significant due to the chronic course and its consequent recurrent infections. This type of neutropenia could be caused by various conditions, such as Kostmann syndrome, Cyclic neutropenia, Shwachman-Diamond syndrome, Myelokathexis, reticular dysgenesis, Dyskeratosis congenital, Immunodeficiency syndromes, and Metabolic diseases (5).

To the best of our knowledge, there is no published report from northwest Iran on the etiology of congenital neutropenia. The current study describes the clinical and laboratory findings of patients with congenital neutropenia from Tabriz Children's Hospital, northwestern Iran.

Materials and Methods

Medical records of 280 patients with neutropenia, who had been admitted to Tabriz Children's Hospital during a 3-year-period (2011-2014), were reviewed in this study, so as to determine the clinical and laboratory findings of congenital neutropenia in the northwest of Iran. These data have been collected through interviewing the patients and their parents and reviewing their medical documents. This study was reviewed and approved by the Ethical Committee of the Faculty of Medicine Tabriz University of Medical Sciences.

In the current study, neutropenia was defined as a significant decrease in the absolute neutrophil count (ANC) of circulating neutrophils in the blood, estimated by the multiplication of the total blood cell count by the percentage of neutrophils plus bands indicated in the differential cell count (6). Based on the ANC, the severity of neutropenia has been subdivided to mild, 1000 to 1500/mm^3; moderate, 500 to 1000/mm^3; and severe, less than 500/mm^3 (6). The leukopenic pattern was defined as a reduced number of white blood cells (<4000/mm^3) (7).

The diagnosis of conditions associated with neutropenia was based on frequent CBC and bone marrow aspiration results. Inclusion criteria were: (1) ANC below 1500/mm^3; (2) informed consent prior to enrollment; (3) follow-up of at least 1 year from the first low ANC; and (4) normal hemoglobin and platelet counts at diagnosis.

Other conditions associated with neutropenia, including infection-related neutropenia, neutropenia related to medications, leukemia, metastatic diseases, nutritional conditions such as marasmus, and immune neutropenia were excluded in this study.

SPSS statistical software package, version 16.0 (SPSS Inc, Chicago, IL, 2007) was used for data analysis.

Results

Characteristics of patients

Thirty-one patients with congenital neutropenia (17 female and 14 male) out of 280 neutropenic patients were reviewed in this investigation. Other 249 patients were excluded due to transient neutropenia, which was mostly associated with cancer chemotherapy (168 cases) and infectious diseases (81 cases). All 31 patients recruited in the current investigation, originated from the cities in northwestern Iran, comprising Tabriz, Ardebil, Malekan, Pars Abad, Mianeh, Basmenj, Oskou, Bookan, Hadishahr, Maragheh, Orumieh, Mianeh Makou, Shahin Dejh, Maragheh, and Mahabad. The mean age of patients with congenital neutropenia was 46.21±37.92 months. The median age for the first manifestation was 13.16±12.48 months. Congenital neutropenia was associated with immunodeficiency syndromes in 30 cases, including combined immunodeficiency (CID) in 8 cases, severe congenital neutropenia (SCN) in 6 cases, common variable immunodeficiency (CVID) in 4 cases, and severe combined immunodeficiency (SCID) in 2 cases, as well as a metabolic disorder in one case. During hospitalization, four patients, comprising one with CVID, one with CID, one with SCID and one with organic academia died as a result of recurrent episodes of infections.

Presenting features and clinical manifestations

The most prevalent presenting features were pneumonia (22.6%), diarrhea (16.1%), otitis media (15%), and failure to thrive (9.7%). The most commonly occurred clinical manifestations during the course of disease were recurrent fever in 21 cases (67.7%), otitis media in 13 cases (41.9%), pneumonia in 12 cases (38,7%), and recurrent aphthous stomatitis, lymphadenopathy, and gingivitis in 11 cases (35.5%).

In the current study, neutropenia could be associated with three distinctive categories of primary

immunodeficiency disorders, including T-cell deficiencies in 11 cases (35.6%), the defects in phagocyte function in 10 cases, and the deficiencies predominantly affecting antibody production in 6 cases, together with other well-defined immunodeficiency syndromes in 3 cases, and organic acidemia in one case.

T-Cell deficiencies

The hematological and immunological characteristics of patients with neutropenia associated with T-cell deficiencies are depicted in table 1 and table 2, respectively.

Table 1. Hematological results of patients with congenital neutropenia

Category	Patient	White Blood Cell$^{\Psi}$ (cell/mm^3)	Absolute Neutrophil Count$^{\Psi}$ (cell/mm^3)	Lymphocyte count$^{\Psi}$ (cell/mm^3)	Eosinophil count$^{\Psi}$ (cell/mm^3)	Platelet count$^{\Psi}$ (cell/mm^3)	Hb$^{\Psi}$ (g/dl)	Hematological Abnormalities
T-cell deficiencies	P4	3000	1000	1700	100	219000	12.3	Leukopenia
	P7	4380	480	1840	290	355000	9.5	Anemia
	P8	1890	600	1200	64	352000	8.5	Leukopenia, Anemia
	P9	7960	130	4925	88	575000	9.5	Anemia
	P10	3380	1250	1370	220	230000	13.5	Leukopenia
	P11	3100	1000	1100	270	206000	7.6	Leukopenia, Lymphopenia, Anemia
	P12	7710	890	4900	380	457000	11.2	-
	P15	4000	1000	2300	380	309000	8.5	Anemia
	P17	4600	920	3080	14	170000	12.2	-
	P19	1480	430	650	150	349000	9	Leukopenia, Lymphopenia, Anemia
	P20	5050	1470	2960	90	279000	11.8	-
	P23	2390	400	580	502	178000	8.9	Leukopenia, Lymphopenia, Eosinophilia, Anemia
	P25	2730	1160	1500	100	321000	12	Leukopenia
Phagocyte defects	P1	6550	540	3850	590	637000	9.3	Anemia, Eosinophilia, Thrombocytosis
	P6	5260	300	4460	30	154000	12	-
	P9	7960	130	4925	88	575000	9.5	Anemia, Eosinophilia, Thrombocytosis
	P14	5650	960	4230	10	356000	7.6	Anemia
	P21	4900	640	3700	59	465000	10.7	Anemia
	P26	5270	540	4130	80	355000	12.7	-
	P27	7450	670	4180	180	380000	10.8	Anemia
	P29	6300	450	5270	110	381000	10.1	Anemia
	P30	5012	231	4160	470	359000	12.5	-
	P31	4740	450	4080	120	410000	12	-
Antibody production deficiencies	P2	8300	270	5300	100	384000	11.6	-
	P3	7000	800	4500	50	220000	8.5	Anemia
	P5	3770	990	2240	37	150000	8.4	Anemia, Leukopenia
	P13	5200	1430	3420	190	320000	11.2	Anemia
	P16	5410	1400	3380	228	162000	13.4	-
	P28	6200	1300	4400	286	222000	12.7	-
Other etiologies	P10	3380	1250	1370	220	230000	13.5	Leukopenia
	P18	4900	530	3230	480	591000	8.4	Anemia, Eosinophilia, Thrombocytosis
	P22	3800	1200	2100	-	195000	10.6	Anemia, Leukopenia
	P24	5990	790	3480	70	556000	9.8	Anemia, Thrombocytosis

Ψ At the time of diagnosis

Table 2. Immunological results of patients with congenital neutropenia

Category	Patient	IgA$^{\Psi}$ (mg/dl)	IgM$^{\Psi}$ (mg/dl)	IgG$^{\Psi}$ (mg/dl)	IgE$^{\Psi}$ (mg/dl)	CD3 (%)	CD4 (%)	CD8 (%)	CD19 (%)	CD56 (%)
T-Cell deficiencies	P4	123	92.5	1280	614	85	28	49	6	23
	P7	312	208	1700	28.2	60	29	32	10	22
	P8	25	28	150	1	31	16	15	2	6
	P11	54	75	467	-	75	11	45	20	12
	P12	184	209	1684	86	57	14	43	23	15
	P15	<60	170	624	46	32	22	9	5	12
	P17	63	360	580	2.4	53	6	40	18	10
	P19	<0.6	77	593	23.2	28	17	5	20	28
	P20	79	113	722	97	67	28	26	17	9
	P23	20	40	100	2	20	2	4	31	14
	P25	23	19	232	130	56	9	46	30	7
Phagocyte defects	P1	317	250	1895	35.8	57	42	15	35	2
	P6	213	129	1154	34.4	61	37	24	30	2
	P9	115	142	88	353	58	43	13	33	5
	P14	40	73	927	17	57	31	22	16	24
	P21	177	100	1500	38	65	30	27	15	17
	P26	58	48	592	28	64	40	24	25	7
	P27	39	45	502	21	62	36	19	24	4
	P29	63	78	500	18.2	70	42	28	14	7
	P30	100	75	120	30	66	43	23	18	5
	P31	120	70	700	80	59	-	20	10	12
Antibody production deficiencies	P2	35	26	280	0.5	79	24	55	3	10
	P3	10	15	350	0.4	75	25	40	6	5
	P5	<0.36	12	228	<1.13	91	28	58	4	4
	P13	8	74	739	21	63	26	36	19	5
	P16	<5	28	386	0.1	57	23	35	9.4	5
	P28	<9	<5	<35	0.5	73	41	32	0.5	4
Other etiologies	P10	10	208	500	1	54	14	36	9	15
	P18	1.6	2.9	15	232	61	43	17	27	9
	P22	68	76	602	26	56	34	18	29	12
	P24	38	40	516	28	62	42	20	21	5

Reference values for IgG (mg/dl): 1–5 years, 345–1,236; 6–10 years, 608–1572; >10 years, 639–1349.Reference values for IgM (mg/dl): 2–8 years, 43–207, 9–10 years, 52–242; >10 years, 56–352. Reference values for IgA (mg/dl): 2–5 years, 14–159; 6–10 years, 33–236; >10 years, 70–312.
$^{\Psi}$ At the time of diagnosis

In the present study, neutropenia was most commonly reported in patients with T-cell deficiencies (7 female and 4 male) with the mean age of 52.8 months, and the median age of 7.6 months for the first presentation. The median age at the time of diagnosis was 35 months, with a median diagnosis delay of 27.4 months. Parental consanguinity, which is defined as two partners having at least one common ancestor, with the ancestor being no more distant than a great great grandparent and the marriage between one person and a third cousin or a closer relative for descendants of the same generation, was present in seven patients. The mean number of neutrophil count in this group of patients was 850 cells/mm^3 (range, 400-1470/mm^3). Severe neutropenia was observed in 3 patients, while in 3 and 5 cases, moderate and mild neutropenia was detected, respectively. Laboratory analysis revealed the following hematologic abnormalities: leukopenia in seven cases (63.6%), lymphopenia in three cases (27.2%), anemia in seven cases (63.6%), and eosinophilia in one case.

Bone marrow studies indicated a myeloid maturation arrest in 4 cases (P12, P19, P23, P25) as well as a decrease in a myeloid cell line in one case (P8); while normal cellularity was reported in 2 cases (P7, P17). Bone marrow examination was not accomplished in the other 4 patients.

Phagocyte defects

Immunodeficiency disorders caused by defects of phagocytes function were the second frequent type of primary neutropenia in our patients (6 males and 4 females), with the mean age of 31.2 months. The mean age at onset was 14 months, and the mean age at diagnosis was 21 months, with a diagnosis delay of 7 months. Parental consanguinity was present in two patients. The mean neutrophil count was 495 cells/mm^3 (range, 130-960/mm^3). Based on the classification of neutropenia, 5 patients suffered from moderate, and 5 from severe neutropenia, at the time of diagnosis. Laboratory analysis indicated anemia in 6 cases (63.6%), concomitant eosinophilia and thrombocytosis in 2 cases with the normal leukocyte count (Table 1). Bone marrow studies showed a decrease in myeloid cell line in 7 cases (P1, P9, P21, P27, P29, P30, P31), the arrest of myeloid

maturation in one case (P26) and the normal activity of bone marrow in 2 cases (P6, P14). Normal immunoglobulin and flow cytometry results were reported in this group of patients (Table 2).

Antibody production deficiencies

The third frequently presented type of primary neutropenia in our patients was antibody production deficiency, presented in 3 females and 3 males, with the mean age of 49.2 months. The mean age of the first presentation of disease was 15.6 months, and the mean age of diagnosis was 37.2 months, with 20.4 months of diagnosis lag. The mean neutrophil count was 1111 cells/mm^3 (range, 270-1430/mm^3). According to the neutropenia classification, one patient was diagnosed to have severe neutropenia, while 1 and 4 cases were known to suffer from moderate and mild neutropenia, respectively (Table 1). Consanguineous marriage was reported in the parents of 4 cases. Laboratory analysis showed anemia in three cases (P3, P5, P13) and leukopenia in one case (P5) (Table 1). Juvenile idiopathic arthritis has been recorded in two patients. The evaluation of bone marrow aspirate in two cases (P2 and P5) revealed the normal cellularity. Bone marrow analysis was not performed in the other four cases because of the establishment of a final diagnosis. All patients are known to have decreased immunoglobulin levels (Table 2).

Other etiologies

The results of hematological and laboratory analysis of patients with ataxia telangiectasia (P10), hyper IgE syndrome (P18), organic acidemia (P22) and glycogen storage disease type Ib (P24) are illustrated in table 1 and table 2, respectively.

In the present study, one case of ataxia telangiectasia (P10) with a diagnosis at 18 months of age was documented. The laboratory analysis of this patient showed mild to moderate neutropenia and a decreased IgA, IgG, and IgE levels.

The patient with a diagnosis of hyper IgE syndrome (P18) was a female, with consanguineous marriage in her parents. Her condition was diagnosed at the age of 6 months due to recurrent pneumonia. The laboratory analysis showed anemia and eosinophilia.

The bone marrow aspirate analysis divulged decreased myeloid counts in P18, but normal cellularity in both P22 and P24.

Discussion

Neutropenia is a relatively frequent hematological abnormality in childhood, characterized by the decreased absolute neutrophil count. It has been recently suggested that the disorders of granulocytopoiesis, ribosomal function, vesicular transport, metabolism, and immune function could lead to congenital neutropenia (8). A number of the myeloid and lymphoid primary immunodeficiency diseases (PIDDs), which are relatively rare disorders with an unusual susceptibility to infections, have associated neutropenia (9), as an isolated complication and in the context of the underlying disease (10). Notwithstanding the fact that neutropenia may accompany any of the primary immunodeficiency diseases as a consequence of either an autoimmune disease or an intercurrent infection (11), the vast majority of investigations have focused on a limited number of disorders, including X-linked agammaglobulinemia, cartilage-hair hypoplasia, common variable Immunodeficiency, Dubowitz syndrome, Griscelli syndrome, hyper IgM syndrome, selective IgA deficiency, reticular dysgenesis, and WHIM (warts, hypogammaglobulinemia, infections, and myelopathies), in which neutropenia is a frequent occurrence and a prominent part of the patient's clinical picture (11). Severe infectious complications are overall more frequent in genetic neutropenias than in acquired neutropenias. In order to achieve more diversified and nuanced treatment approaches, additional clinical observations and investigations into both the pathophysiology and the management of hereditary neutropenia, such as those occurring in some PIDDs, are required. The present study aimed at describing the clinical and laboratory findings of 31 patients with congenital neutropenia from northwestern Iran.

The estimated occurrence of PIDDs in the Turk ethnic group, living in northwestern Iran, had been recently estimated to be about 24 per 100,000 live births. Combined T and B cell immune deficiencies, comprising severe combined immunodeficiency (32.2%), ataxia-telangiectasia (22.0%) and common variable immunodeficiency (18.6%) were shown to be the most prevalent form of PIDD in this region (12). Our results revealed congenital neutropenia to be mostly associated with primary immunodeficiency disorders (PIDDs) in northwestern Iran (96.77%). The most common PIDDs companying with congenital neutropenia were found to be combined immunodeficiency (26.67%), severe congenital neutropenia (20%), common variable immunodeficiency (13.33%), severe combined immunodeficiency (6.67%), ataxia-telangiectasia (3.33%), and hyper IgE syndrome (3.33%).

Ina study conducted by Rezaei *et al*., records of 26

patients with inherited neutropenia concomitant with primary immunodeficiency disorders, including cyclic neutropenia (8 patients), Shwachman-Diamond syndrome (7 patients), Kostmann syndrome (6 patients), and Chediak-Higashi syndrome (5 patients) were reviewed. The mean absolute neutrophil count of patients at the first visit was 398.2±259.3/mm3 (range 74–1152/mm^3). The most frequent presenting complaints in these 26 patients were oral ulcer, otitis, pneumonia, diarrhea, cutaneous abscess, and oral candidiasis. They reported the most common infections, in descending order of frequency, to be otitis media, abscesses, pneumonia, oral ulcers, acute diarrhea, cutaneous infections, oral candidiasis, and periodontitis (13). In another investigation, the records of 56 neutropenic patients among 474 registered patients with PIDDs had been reviewed by Rezaei *et al.*, . They showed that the most common disorders associated with neutropenia were Shwachman-Diamond syndrome, cyclic neutropenia, Kostmann disease, Chediak-Higashi syndrome, hyper IgM syndromes, severe combined immunodeficiency, hyper IgE syndrome, and common variable immunodeficiency in Iranian population (14).

An increased susceptibility to infections was discovered in our patients. Respiratory infections were the most prevalent type of involvement in these patients. Also, a highly increased incidence of gastrointestinal involvement as the first manifestation, as well as the elevated incidence of oral manifestations during the disease course was detected. The clinical history and examination of the peripheral blood smear are the paramount diagnostic keys in patients with unexpected neutropenia. Recurrent infections insinuate significant neutropenia. Prevalent sites of infection comprise the oral cavity and mucous membranes, presenting as mouth ulcers and periodontitis, the skin, presenting as rash, ulcerations, and abscesses, as well as the perirectal and genital areas (6). Thus, examination of the oral cavity, skin, and perianal region, is indispensable, to assess the clinical impact of neutropenia. However, patient's quality of life and life expectancy will be good with the help of intent physicians and dentists (15).

Severe or persistent infections should always raise a suspicion, which merits further assessment of an underlying immune deficiency syndrome and neutropenia. Regardless of the currently available management strategies, a delay in diagnosis may entail more pronounced complications, which may be widespread and negatively affect both morbidity and mortality (16). The key to the successful diagnosis and management of patients with immunodeficiency is known to be the patients' timely referral to a clinical immunologist (17). It could set the stage for a better understanding of the pathological and physiological processes, and offer incipient opportunities to treat these conditions.

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