

# Etiological causes and prognosis in children with neutropenia

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## ABSTRACT

**OBJECTIVE:** Neutropenia is defined as an absolute neutrophil count (ANC) below 1500/mm<sup>3</sup> in the peripheral blood and is a common condition in childhood. In this study, underlying etiological causes and prognoses in children in follow-up due to neutropenia were analyzed to form a guide for physicians working in primary health care institutions.

**METHODS:** The medical records of pediatric patients who were followed up as inpatients or outpatients due to neutropenia between October 2014 and October 2017 were reviewed retrospectively.

**RESULTS:** A total of 94 patients were included in the study with a median age of 24 (8–77) months. The median ANC at the time of admission was 600 (300–970)/mm<sup>3</sup>. The ANC was 0–500/mm<sup>3</sup> in 34 patients (36.2%), 500–1000/mm<sup>3</sup> in 36 patients (38.3%), and 1000–1500/mm<sup>3</sup> in 24 patients (25.5%). Of the total, 43 patients (45.7%) were followed up as inpatients and 51 (54.3%) were followed up as outpatients. Fifty-five patients (58.5%) were diagnosed with post-infectious neutropenia. The most common focus of infection was the upper respiratory airway (38.4%). The etiological cause could not be identified in 23 (24.6%) patients, neutropenia developed during drug use in 6 patients (6.3%), 5 patients (5.3%) were diagnosed with Vitamin B12 deficiency (Vitamin B12 level: 168 [129–174] pg/ml, the levels were studied in 48 patients), 2 patients (2%) were diagnosed with chronic benign neutropenia, 1 patient (1.1%) was diagnosed with immune deficiency, 1 patient (1.1%) was diagnosed with autoimmune lymphoproliferative syndrome, and 1 patient (1.1%) was diagnosed with hemophagocytic lymphohistiocytosis secondary to a previous infection. No patient was diagnosed with congenital neutropenia. A total of 91 patients (96.8%) recovered from the neutropenia. Neutropenia did not improve in 3 patients (3.2%). One patient was lost due to infection.

**CONCLUSION:** Etiological cause can be shown in approximately 75% of neutropenic children. The most common etiological cause is infection. Drug use, nutritional deficiencies, and chronic benign neutropenia are less common causes of neutropenia. The clinical course is largely benign and the mortality rate is very low.

*Keywords:* Child; etiology; neutropenia; prognosis.

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Polymorphonuclear cells, known also as neutrophils, are the largest group of leukocytes in peripheral blood. They are produced from multipotent myeloid stem cells through a process of granulopoiesis in the bone marrow [1]. They are a part of the innate immunity against bacteria and fungi, and play an important role in initial defense of the host against the infection [2].

The lower normal limit for absolute neutrophil count (ANC) in the 1<sup>st</sup> week of life is 5000/mm<sup>3</sup>, and this value decreases to 1000/mm<sup>3</sup> between the 2<sup>nd</sup> week of life and 1 year of age [3]. After the age of 1 year, an ANC below 1500/mm<sup>3</sup> is defined as neutropenia, between 1000 and 1500/mm<sup>3</sup> as mild, between 500 and 1000/mm<sup>3</sup> as moderate, and below 500/mm<sup>3</sup> as

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severe neutropenia [3]. Certain populations (e.g., African-Americans, Yemenite Jews, Ethiopians, and certain Arabs) normally have slightly lower white blood cell count and ANC values [4].

Neutropenia can be classified as congenital or acquired. Congenital neutropenia is a heterogeneous hereditary group of disorders that are characterized by intermittent episodes or continuous severe or moderate neutropenia persisting for at least 3 months, and can develop at any stage of the proliferation and maturation phases of neutrophils, secondary to genetic causes. Although it occurs only rarely, congenital neutropenia is a significant condition that causes recurrent infections and has a chronic course, and exhibits autosomal recessive inheritance in the majority of cases [2, 5]. Acquired neutropenia is more common than congenital neutropenia, with the most common causes being infections, drugs, and chronic benign neutropenia in infancy and childhood. It is believed that the majority of cases defined as chronic benign neutropenia in infancy and childhood represent an autoimmune neutropenia that is parallel to childhood idiopathic thrombocytopenic purpura [2]. Chronic benign neutropenia is the most common form of chronic neutropenia in the pediatric age group, occurring in approximately 1/100,000 children/year [6, 7], with the median age at diagnosis being 7–9 months [8–10]. Spontaneous remission is observed in almost all patients, and the median duration of neutropenia is 20 months [9]. The likelihood of spontaneous remission is higher in children younger than 9 months at the time of diagnosis, and this likelihood decreases with increasing age [2]. Apart from these, bone marrow involvement, nutritional causes, immunological disorders, metabolic disorders, autoimmune lymphoproliferative syndrome, and Evans syndrome are other causes of acquired neutropenia [2, 5].

The present study determines the underlying etiological causes, clinical course, and prognosis in children followed up at our hospital due to neutropenia.

## MATERIALS AND METHODS

The present study retrospectively reviewed the medical records of patients who were under follow-up as inpatients or outpatients at the pediatric hematology and oncology clinic between October 2014 and October 2017. Age, gender, blood count on admission, physical examination findings, diagnoses established after laboratory tests, recovery in neutrophil counts during follow-up, time of

### Highlight key points

- Because there are various causes of childhood neutropenia, making the determination of the possible cause in a child is very difficult for pediatricians.
- Although the results of our study do not reflect the true distribution of causes in the pediatric population, the most common ethological causes we found were infections (58.5%) and various medications (6.3%).
- When evaluating a child with neutropenia, the most common etiological reasons should be considered first, and if there are atypical physical examination findings and accompanying cytopenias such as anemia and thrombocytopenia, a detailed laboratory examination should be performed.

recovery, and changes in the disease course were garnered from the patient charts. Newborns, patients with neutropenia accompanied by anemia and/or thrombocytopenia, and patients with neutropenia secondary to chemotherapy were excluded from the study. Infections were diagnosed using anamnesis, physical examination, and clinical and laboratory findings. A throat culture was taken from patients with lower and upper respiratory tract infections. Gaita microscopy was studied for patients with gastroenteritis. For the diagnosis of lower respiratory tract infections, a radiological assessment was made in addition to cultures. No specimen was taken from the lower respiratory tract since our patients were at very young age. Previous blood counts were evaluated to determine whether neutropenia had a new onset or previously existed. It was assumed that neutropenia had newly developed in patients without a previously performed blood count. This study was approved by the Eskisehir Osmangazi University Non-Interventional Research Ethics Committee (ethic approval no: 23) and was conducted in accordance with principles of Helsinki Declaration.

### Statistical Analysis

Statistical analyses were performed using statistical package software (SPSS 21, Chicago, IL, USA). The quantitative characteristics of the patients are shown as numbers (n) and frequencies (%) in the tables. The numerical variables are expressed as median and interquartile distribution (Q1–Q3) range.

## RESULTS

A total of 94 children were included in the study, of which 49 (52%) were female and 45 (48%) were male, and the mean age of the patients was 24 (8–77) months. On ad-

**TABLE 1.** Clinical characteristics and laboratory parameters of the patients

|  |                           |
|--|---------------------------|
| Gender (F/M)                               | 49/45                     |
| Age (month)                                | 24 (8–77)                 |
| Hemoglobin (g/dl)                          | 11.9 (10.8–12.6)          |
| White blood cell count (/mm <sup>3</sup> ) | 5000 (2900–6850)          |
| ANC (/mm <sup>3</sup> )                    | 600 (300–970)             |
| Lymphocyte count (/mm <sup>3</sup> )       | 3300 (1800–5250)          |
| Monocyte count (/mm <sup>3</sup> )         | 500 (300–700)             |
| Platelet count (/mm <sup>3</sup> )         | 259.000 (199.500–389.000) |
|  | (%)                       |
| ANC: 0–500 (/mm <sup>3</sup> )             | 36.2                      |
| ANC: 500–1000 (/mm <sup>3</sup> )          | 38.3                      |
| ANC: 1000–1500 (/mm <sup>3</sup> )         | 25.5                      |

Numerical variables are expressed as median and interquartile distribution (Q1–Q3). ANC: Absolute neutrophil count.

mission, median hemoglobin level, white blood cell count, ANC, lymphocyte count, monocyte count, and platelet count were 11.9 (10.8–12.6) g/dl, 5000 (2900–6850) /mm<sup>3</sup>, 600 (300–970) /mm<sup>3</sup>, 3300 (1800–5250) /mm<sup>3</sup>, 500 (300–700) /mm<sup>3</sup>, and 259,000 (199,500–389,000) /mm<sup>3</sup>, respectively. The ANC was 0–500/mm<sup>3</sup> in 34 patients (36.2%), 500–1000/mm<sup>3</sup> in 36 patients (38.3%), and 1000–1500/mm<sup>3</sup> in 24 patients (25.5%). The clinical characteristics and laboratory parameters of the patients are presented in Table 1.

Of the total, 43 patients (45.7%) were followed up as inpatients and 51 (54.3%) were followed as outpatients. The median length of hospital stay was 16 (5–30) days for hospitalized patients. Blood culture was performed on 39 out of 43 patients, urine culture was performed on 36 patients. Bacterial growths were identified in the blood cultures of two patients and in the urine cultures of two patients. *Staphylococcus hominis* was isolated in the blood culture of one patient, *Pseudomonas aeruginosa* was isolated in another patient, and *Enterococcus faecium* was isolated in the urine culture of two patients (Table 2).

Of the total, 21 patients (22.3%), who had long-term persistent neutropenia (duration of neutropenia ≥3 months) or severe neutropenia accompanied by intractable fever, underwent bone marrow aspiration to rule out congenital neutropenia and leukemia. Leukemia was ruled out in all patients. Maturation arrest was observed in the bone marrow of three patients. HAX-1, ELANE gene mutation analysis was performed in 21 patients, but no mutation was detected in any patient.

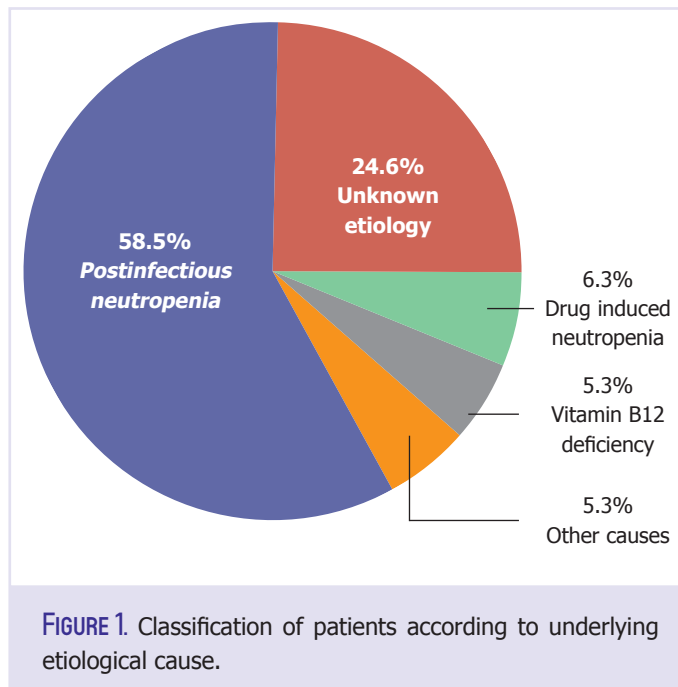
**TABLE 2.** Etiological causes and isolated infectious agents

| Etiological causes                      | %    |
|---|------|
| Post-infectious neutropenia             | 58.5 |
| Focus of infection                      |      |
| Upper respiratory tract*                | 38.4 |
| Gastroenteritis                         | 6.4  |
| Lower respiratory tract                 | 4.3  |
| Urinary tract infections**              | 3.2  |
| Otitis                                  | 2    |
| Oral mucositis                          | 2    |
| Conjunctivitis                          | 1.1  |
| Bronchitis                              | 1.1  |
| Unknown etiology                        | 24.6 |
| Drug-induced neutropenia                | 6.3  |
| Vitamin B12 deficiency                  | 5.3  |
| Other causes                            | 5.3  |
| Chronic benign neutropenia              | 2    |
| Immune deficiency                       | 1.1  |
| Autoimmune lymphoproliferative syndrome | 1.1  |
| Hemophagocytic lymphohistiocytosis      | 1.1  |

\*: Influenza Type A virus in nasopharyngeal specimens by polymerase chain reaction (PCR) test and *Pseudomonas aeruginosa* in blood culture from one patient, *Staphylococcus hominis* in blood culture from one patient; \*\*: *Enterococcus faecium* in urinary culture from two patients.

### Etiological Causes

Of the total, 55 patients (58.5%) were diagnosed with neutropenia secondary to an infection and no further investigation was carried out. The focus of infection was the upper respiratory tract in 36 patients (38.4%), gastroenteritis in 6 patients (6.4%), lower respiratory tract infections (pneumonia in four and bronchitis in one) in 5 patients (5.3%), urinary tract infections in 3 patients (3.2%), otitis in 2 patients (2%), oral mucositis in 2 patients (2%), and conjunctivitis in 1 patient (1.1%). Of these patients, nine had a history of metamizole use. We included these patients in the post-infectious neutropenia group as they had infections at admission. Further investigation was performed to reveal the etiology in patients (39 patients, 41.4%) without signs of infection. The etiological cause could not be identified in 23 (24.6%) patients. It was found that neutropenia developed during drug use (phenytoin in two patients, valproic acid in one patient, colchicine in one patient, and metamizole sodium in two patients) in 6 patients (6.3%), and the neutropenia in these cas-



es was considered to be associated with this. Of the total, 5 patients (5.3%) had Vitamin B12 deficiency (Vitamin B12 level: 168 [129–174] pg/ml; Vitamin B12 was studied in 48 patients) and 5 patients (5.3%) had other causes. Of these five patients, 2 (2%) were diagnosed with chronic benign neutropenia, 1 patient (1.1%) was diagnosed with immune deficiency, 1 patient (1.1%) was diagnosed with autoimmune lymphoproliferative syndrome, and 1 patient (1.1%) was diagnosed with hemophagocytic lymphohistiocytosis secondary to a previous infection. Classification of patients according to underlying etiologic cause is shown in Figure 1. Underlying etiological factors and isolated infectious agents are provided in Table 2.

### Prognosis

On the total, 91 patients (96.8%) recovered from neutropenia. The mean time for recovery from neutropenia in patients with an infectious cause was 1 (1–3) month. All patients aside from one completely recovered from neutropenia. The mean recovery time from neutropenia in patients without a detectable etiological cause was 1 (1–2.75) month. Patients who were found to have neutropenia associated with drug use and Vitamin B12 deficiency recovered from neutropenia after the discontinuation of the responsible drug and Vitamin B12 replacement therapy, respectively; 3 patients (3.2%) did not recover from neutropenia; and one patient who was

diagnosed with immune deficiency dropped from the follow-up to continue their follow at in another center. The patient diagnosed with autoimmune lymphoproliferative syndrome developed hemolytic anemia and underwent plasmapheresis during the follow-up period, and this patient was referred to another center for bone marrow transplantation. The single patient who was regarded as having neutropenia secondary to an infection died of viral pneumonia (influenza Type A virus) and subsequent bacterial (*P. aeruginosa*) sepsis. Another patient diagnosed with Hemophagocytic lymphohistiocytosis (HLH) developed thrombocytopenia during the follow-up, and required multiple antibiotherapies and immunosuppressive therapy, and the clinical and laboratory findings were seen to recover completely after therapy.

### DISCUSSION

Post-infectious neutropenia is the most common cause of neutropenia in childhood and can develop as a result of viral, bacterial, or parasitic infections [11–13]. In a study investigating the prevalence of leukopenia in inpatients in a hospital in the province of Adana, the prevalence of leukopenia was found to be 1.03%, and neutropenia was detected in 66.7% of these patients. Infections and drugs were identified as the most common causes of leukopenia/neutropenia [14]. Sheen et al. [15] reported bronchopneumonia and non-specific fever to be the most common reasons for hospital admission in children with moderate or severe neutropenia. Post-infectious neutropenia was found to be the most common etiological cause in the present study. A previous study conducted at a university hospital in France reported that the most common cause of neutropenia was infections (37.8%) among children with isolated neutropenia, and 90.3% of the infectious episodes of neutropenia were viral [16]. The study by Husain et al. reported that infectious agents were identified in 55% of neutropenic children, 93% of such agents were viral, neutropenic children did not develop serious bacterial infections, and a bacterial agent was isolated in 7% of the patients (urinary tract infections with *Escherichia coli*) [17]. In the present study, a bacterial agent was isolated in a total of 4 (4.2%) patients (urine culture, 2 patients; blood culture, 2 patients). The patient with *P. aeruginosa* isolated in blood culture died, while other three patients recovered.

Viral infections are the most common cause of neutropenia, within influenza A and B, adenovirus, respira-

tory syncytial virus, enteroviruses, human herpes simplex virus 6, rubeola, rubella, and varicella counted among the viruses that cause acute, transient neutropenia [11–13]. Neutropenia is of short duration and temporary in postinfectious neutropenia [12]. Another study reported neutropenia lasting more than a year in approximately 6% of children with post-infectious neutropenia, and found that the duration of neutropenia was remarkably higher in cytomegalovirus-associated neutropenia than in influenza and Epstein-Barr virus-associated neutropenia [15]. The underlying mechanisms include the redistribution, sequestration, aggregation, and destruction of neutrophils by antibodies in the circulation [12]. Viral infections can cause both temporary suppression and temporary aplasia associated with the depletion of hematopoietic stem cells and stromal cells with the effect of Type I interferons [13]. The causative agent could not be isolated as nasopharyngeal swabs were not routinely obtained for viral infections due to the high cost of the test. Viral infections are diagnosed by assessing clinical and laboratory findings together.

The second most common etiological factor was drug-related neutropenia in the present study. The prevalence of drug-related neutropenia in children is unknown, although the present study found that neutropenia developed in 6.4% (6 patients) of the patients during drug use, and all recovered from neutropenia after the discontinuation of the drug. Drug-related neutropenia refers to an idiosyncratic reaction against the drug that is different from drug-related aplastic anemia, in which other cell lines are also affected, and neutropenia occurring during anticancer therapy [2]. Non-chemotherapy idiosyncratic drug-induced neutropenia (IDIN) is a relatively rare but potentially fatal disorder that occurs in susceptible individuals, with an incidence of 2.4–15.4 cases/million populations [18]. The IDIN-associated mortality rate is estimated to be 5% [19]. There are a very few reports reporting on the prevalence of IDIN in pediatric patients, although one study reported an annual incidence of 3.92 cases/10,000 pediatric patients [20]. The prevalence of IDIN is higher in patients older than 65 years, and mortality increases with age [21, 22]. Many commonly used drugs can cause idiosyncratic neutropenia or agranulocytosis. It has been reported that the drugs with the highest potential in this respect include deferiprone, clozapine, trimethoprim, sulfamethoxazole, and rituximab [2]. Although the underlying mechanism is unknown in the majority of drug-related neutropenia, studies have shown that it develops as a re-

sult of the toxic suppression of neutrophil production or the immune-mediated destruction of mature cells [23, 24]. Metamizole sodium is an effective analgesic and antipyretic drug that is commonly used in Turkey and around the world that has serious hematological side effects, such as agranulocytosis and aplastic anemia. It is estimated the global incidences of metamizole-related agranulocytosis number around 7.000 cases/year [25]. There are no data on the prevalence of metamizole-related neutropenia and agranulocytosis in Turkey, although one study conducted in Elazig reported that the incidence of metamizole-related agranulocytosis is 1 pediatric case/10.000 hospital admissions, although this study was not designed specifically to determine the incidence [26]. In the present study, some patients recovered from neutropenia after discontinuing metamizole, but aside from these patients, there were a very few patients with pancytopenia who were considered to be secondary to metamizole use.

Autoimmune neutropenia in infancy and childhood is divided into two groups, being the primary/isolated and secondary/associated forms [27]. Primary/isolated autoimmune neutropenia is referred to also as chronic and develops as a result of sensitization to the antigens specific to neutrophils that are not found in other hematopoietic cells. Antineutrophil antibodies can be detected in many patients and often target (human neutrophil antigens 1 FcγRIII) [2]. An examination of bone marrow may reveal normal or increased myelopoiesis and sometimes a decrease in mature neutrophils or maturation arrest in the earlier stages [2]. Bacterial infections often have a mild course and respond to standard antibiotic regimens [6, 9, 28]. Although the ANC is found to be below 500/mm<sup>3</sup> in more than two-thirds of patients, only 12–20% of patients develop severe infections [8, 29]. An increase in neutrophil count and monocytosis is observed in approximately 25% of patients [8, 28], and this probably contributes to the mild clinical course of the disease [27]. In the present study, 2 patients (2%) were diagnosed with chronic benign/autoimmune neutropenia, with neutrophil counts remaining constantly below 500/mm<sup>3</sup> and none suffering infections severe enough to require hospitalization. One patient recovered from neutropenia at the age of 4 and another at the age of 2. The avoidance of severe infection in these patients can be attributed to their normal bone marrow reserves. Chronic/benign autoimmune neutropenia of infancy and early childhood is a relatively common condition.

The present study found the frequency of chronic benign neutropenia, which is also called autoimmune neutropenia, to be 2%. The absence of patients diagnosed with congenital neutropenia and the low number of patients with chronic benign neutropenia may be associated with the characteristics of our center, since our pediatric hematology and oncology clinic provides medical care to approximately 3–4% of the pediatric population in Eskişehir Province.

Despite all tests, the underlying etiological factor may not be identified in children with isolated neutropenia. A previous study from France reported this rate to be 32% [16]. The present study also could not identify the etiological factor in 24.5% of the study patients.

Neutropenia is also observed in nutritional disorders such as anorexia nervosa and marasmus, where severe protein deficiencies exist [2]. Vitamin B12 and folic acid deficiencies cause ineffective granulopoiesis together with megaloblastic bone marrow changes [2, 12]. Although it has been reported that anemia and sometimes thrombocytopenia develop together with neutropenia in the event of nutritional deficiency, neutropenia developed in the absence of anemia and thrombocytopenia in our patients with Vitamin B12 deficiencies.

## Conclusion

The underlying etiological factors and clinical course differ in childhood neutropenia. Childhood neutropenia should not always be considered as a sign of malignancy. It must be kept in mind that infections are the underlying cause in the majority of patients; however, further tests are expensive and unavailable at every center. Particular attention must be paid to patients with severe bacterial infections, history of frequently recurring infections, and patients with atypical physical examination findings, with further tests planned to include bone marrow examinations.

**Ethics Committee Approval:** The Eskişehir Osmangazi University Non-Interventional Research Ethics Committee granted approval for this study (date: 06.11.2018, number: 23).

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