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Original Article

Clinical spectrum of pediatric neutropenia: mostly benign, but not to be overlooked

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ABSTRACT

Background. Neutropenia is a common laboratory finding in children, therefore it is a common referral reason to pediatric hematology units. This study hypothesizes that most neutropenic children do not require pediatric hematology consultation, and that key clinical indicators can guide the need for referral.

Methods. Medical records of 180 patients who were admitted to a tertiary reference center, were evaluated in terms of demographical data, physical examination findings, laboratory findings, and outcome measures. The patients enrolled in the study had newly diagnosed or incidental neutropenia and did not meet the criteria for chronic neutropenia. Neutropenia was classified based on absolute neutrophil count (ANC) as follows: mild (1000–1499/mm^3), moderate (500–999/mm^3), severe (200–499/mm^3), and very severe (<200/mm^3).

Results. Of the 180 patients enrolled, 51.7% were male, with a mean age of 4.8 years (min-max: 1 week- 17 years). 12 patients (6.7%) were diagnosed with congenital neutropenia. The median age for patients diagnosed with congenital neutropenia was 12 months, whereas it was 47 months for those with post-infectious neutropenia (p=0.037). 64.4% of patients had no known prior disease, and 45% were incidentally found to have neutropenia. The average ANC was 732/mm^3, with 26.1% having mild, 47.2% moderate, 19.4% severe, and 7.2% very severe neutropenia. Etiological causes included post-infectious (53.9%), idiopathic/immune (25.6%), congenital (6.7%), and drug-related (6.7%) neutropenia. The median ANC for congenital neutropenia patients was 200/mm^3, and their infection rates were significantly higher than the other groups (p=0.001). The mean follow-up period was 10 months, with 69.4% of patients having normal ANC at the last follow-up.

Conclusions. Despite the increased frequency of neutropenia in childhood, a vast majority of the cases have a benign and transient clinical course.

Key words: pediatric neutropenia, congenital neutropenia, immune neutropenia, post-infectious neutropenia.

Neutropenia is one of the most common causes of referral to pediatric hematology outpatient clinics, defined as a decrease in the number of neutrophils in the peripheral blood. Although the normal values of absolute neutrophil count (ANC) vary according to age and race, the lower limit is considered to be 5000/mm^3 during the first 24 hours of life, 2500/mm^3 for term/near-term neonates 72-240 hours after delivery, 1000/mm^3 for preterm infants, and then 1000/mm^3 during the first year of life. After the first year of life, the lower limit for ANC is regarded as 1500/mm^3.[1-4] The underlying etiology can range from mild to life-threatening conditions. In the clinical evaluation, the presence of a serious underlying bone marrow-related disease and whether the patient has an increased risk of life-threatening infection due to neutropenia are important considerations. Neutropenia can lead to a serious course in immunocompromised

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patients with oncological diagnoses. In contrast, milder and transient conditions may play a role in the etiology of immunocompetent individuals.[3]

Depending whether it lasts shorter or longer than 3 months, neutropenia can be classified as acute or chronic. The etiologic causes of neutropenia can be divided into two main groups; acquired and congenital. Acquired neutropenia is more common than congenital neutropenia.[4] The most common underlying causes are infections, drugs and chronic benign neutropenia. The most common cause of chronic neutropenia in childhood is chronic benign neutropenia and the annual incidence is reported as 1/100,000. In this type of neutropenia, spontaneous remission is observed in almost all patients, within a median duration of 20 months. In addition, nutritional causes, metabolic and immunologic disorders can be listed as other causes of acquired neutropenia. On the other hand, congenital neutropenia represents a heterogeneous group of diseases and is characterized by moderate or severe neutropenia observed in intermittent episodes or persistently. Although rare, it can progress with recurrent infections and life-threatening conditions. The inheritance is autosomal recessive in the vast majority of cases.[5,6]

In the current cohort, we aimed to evaluate the patients with neutropenia who were admitted to our unit, which is a tertiary reference center. Our hypothesis was that the majority of patients referred to pediatric hematology outpatient clinics have benign and reversible causes of neutropenia, which will resolve without the need for follow-up and treatment by a pediatric hematologist.

Materials and Methods

In our study, the medical records of 180 patients who were referred to our clinic between January 2011 and December 2021, a 10-year period, due to neutropenia were assessed. It should be noted that the patients included in this study were referred upon first detection of neutropenia and had not yet fulfilled the diagnostic criteria for chronic neutropenia (defined as neutropenia persisting for more than 3 months). Age, gender, primary complaint and physical examination findings, personal and family histories, laboratory findings on admission and clinical follow-up, infections during follow-up, hospitalizations, drug use, diagnostic tests, diagnoses, whether there is a recovery in neutrophil counts, time of recovery and follow-up results were evaluated.

Neutropenia was classified based on ANC as follows: mild (1000–1499/mm^3), moderate (500–999/mm^3), severe (200–499/mm^3), and very severe (<200/mm^3).[1]Transient neutropenia accompanied by symptoms of infections and/or positive for infectious tests, in the absence of other underlying causes, was defined as infectious-related neutropenia. Immune-mediated neutropenia was also diagnosed with increased mature neutrophils in bone marrow aspiration (BMA) in patients with no accompanying signs and symptoms.

The current study was approved by the Dokuz Eylül University Ethics Committee (ethical approval number: 2022/04-04) and performed in accordance with the principles of Helsinki Declaration.

Statistical analysis

In the present study, clinical results were evaluated using descriptive statistical methods. The quantitative characteristics of the patients are shown with numbers (n) and frequencies (%) in the text and tables. Comparative evaluations between independent groups in terms of hospitalization, need for treatment and frequency of infection were assessed with non-parametric tests. Normal distribution of data was evaluated using the Kolmogorov–Smirnov test. Descriptive statistics; number and percentage for categorical variables; for numerical variables, data that provided normal distribution parameters were given as mean±standard deviation, and for data that

did not comply with normal distribution, they were given as median (minimum-maximum value). Comparison of data was made with Student's t test for variables with normal distribution, and with Mann-Whitney U test for those with non-normal distribution. Pearson chi-square (χ^2) test was used to compare categorical data. The relationship between the parameters was investigated with the Pearson or Spearman correlation test. Factors shown to be effective on the dependent variable were tested with multiple logistic regression analysis to reveal estimated risk ratios. In cases where the dependent variable did not show a normal distribution between groups, the non-parametric test, Kruskal-Wallis test, was applied. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS 22, Chicago, IL, USA).

Results

Of the 180 patients, 87 (48.3%) were female and 93 (51.7%) were male. The mean age at admission was 4.8±4.87 years and the median age was 2.8 years (range: 1 week- 17 years). The median age of the patients diagnosed with congenital neutropenia was 12 months (range: 1 week- 150 months). On the contrary, the median age of the patients with post-infectious neutropenia was 47 months (range 1 month-214 months). The difference between the two groups was statistically significant with a p value of 0.037.

On admission, 116 patients (64.4%) had no known disease before. Eighty-one patients (45%) were referred with incidentally detected neutropenia and had no complaints on admission. The remaining patients were assessed for acute infectious processes and had findings such as a runny nose, fever, and cough. No pathological features were found on physical examination in 83.9% (n=151) of the patients at admission. Only 16 patients (8.8%) had neutropenia before admission. Among these patients, the median first time of neutropenia detection was observed as 3 months (range: 1 month-16 months). Some of these patients were evaluated for etiology in other centers. Of the physicians who referred patients to our unit, 87.8% (n=158) were pediatricians.

The mean ANC was 732±372/mm^3 and the median was 700/mm^3 (range: 100-1400/mm^3) on admission. Considering the ANC categories, 47 patients (26.1%) were in the mild neutropenia group, 85 patients (47.2%) in the moderate, 35 patients (19.4%) in the severe, and only 13 patients (7.2%) were in the very severe neutropenia group. Whole blood count findings and clinical characteristics on admission are presented in Table I. Lymphocytosis was observed in 40% (n=72) of patients on peripheral blood smear. Evaluating the monocyte and eosinophil counts, the mean absolute monocyte count (AMC) was 1265±174/mm^3 for congenital neutropenia patients (n=12, 6.7%), whereas it was 534±336/mm^3 for the others (n=168, 93.3%). The congenital neutropenia group had a mean absolute eosinophil count (AEC) of 652±238/mm^3 whilst the remaining had a mean AEC of 218±326/mm^3. Although an apparent difference was observed, statistical analysis could not be

Table I. Clinical characteristics and laboratory results on admission.

Female gender, n (%)	87 (48.3%)
Age (years)	4.8±4.87
Complaints on admission, n (%)	
No complaints	81 (45%)
Fever	61 (33.8%)
Viral infection	38 (21.1%)
Hemoglobin (g/dL)	11.5 ± 1.39
White blood cell count (/mm^3)	4,970 ± 2,466
Absolute neutrophil count (/mm^3)	732 ± 372
Lymphocyte count (/mm^3)	3,466 ± 2,260
Monocyte count (/mm^3)	583 ± 473
Platelet count (/mm^3)	285,000 ± 139.000
Severity of neutropenia, n (%)	
Very severe (ANC <200/mm^3)	13 (7.2%)
Severe (ANC 200-499/mm^3)	35 (19.4%)
Moderate (ANC 500-999/mm^3)	85 (47.2%)
Mild (ANC 1000-1499/mm^3)	47 (26.1%)

ANC: Absolute neutrophil count.

performed due to the limited sample size of the congenital neutropenia group.

Viral serology tests were obtained in 58.3% (n: 105) of the patients, and was negative in 73.3% (77) of them. Eighteen patients (64.2%) were positive for Epstein-Barr virus, while 3 were positive for cytomegalovirus, 2 for rubella, 1 for toxoplasmosis, 1 for varicella zoster, 2 for rhinovirus and 1 for influenza type B.

BMA was obtained in 60 (33.3%) of 180 patients, revealing an increased number of mature neutrophils in the marrow in 46 patients (25.6%), which supported the diagnosis of immune neutropenia. Of the remaining, 12 (6.7%) disclosed maturation arrest in the myeloid lineage, giving rise to the diagnosis of congenital neutropenia, and 2 were normocellular.

Of the patients, 53.9% (n=97) were diagnosed with post-infectious, 25.6% (n=46) with idiopathic/immune, and only 6.7% (n=12) with congenital neutropenia. In addition, drug-related neutropenia was observed in 12 patients (6.7%), and vitamin B12 deficiency-related neutropenia was observed in 5 patients (2.7%). Underlying rheumatological, genetic, and metabolic diseases such as celiac disease, Tay-Sachs disease, glycogen storage disease type 1b and IgA vasculitis (Henoch-Schönlein purpura) were detected in 4.4% (n=8) of the patients. None of the patients were diagnosed with a malignancy. A detailed summary of etiological causes is present in Table II.

Patients with the diagnosis of congenital neutropenia (n=12) had a median ANC of 200/mm^3 (100-800/mm^3) on admission, whereas the median ANC values for patients diagnosed with post-infectious and immune neutropenia were 800/mm^3 (100-1400/mm^3) and 750/mm^3 (100-1400/mm^3), respectively. This difference was statistically significant ($p<0.001$). Regarding the complaints of the congenital neutropenia group, recurrent fever, skin, gastrointestinal and pulmonary infections were detected. The number of infections (median: 4) of the patients diagnosed with congenital neutropenia was found to be significantly higher than the other groups (p:0.001) in the Kruskal-Wallis analyses. The confirmed diagnoses of congenital neutropenia included 1 patient each of Shwachman-Diamond syndrome, Kostmann syndrome, ELANE-related neutropenia, and G6PC3-related neutropenia. The remaining patients, despite negative results on the genetic panel used in our center, were diagnosed with congenital neutropenia based on decreased myeloid production observed in BMA, increased susceptibility to infections, and the presence of definitive infectious foci. All patients diagnosed with congenital neutropenia received granulocyte colony stimulating factor (G-CSF) therapy.

The mean follow-up period was 10 ±14 months. Ninety-three patients (51.7%) did not need hematological follow-up. The median duration of neutropenia in these patients was 2 months (range: 1 week- 15 months). Twenty-two patients

Table II. Etiological causes of neutropenia in our patients.

Etiological cause	n (%)
Infections	97 (53.9%)
EBV	18 (18.5%)
CMV	3 (3.09%)
Rubella	2 (2.06%)
Toxoplasmosis	1 (1.03%)
Varicella zoster	1 (1.03%)
Rhinovirus	2 (2.06%)
Influenza type B	1 (1.03%)
Undetermined	69 (71.1%)
Idiopathic/immune	46 (25.6%)
Congenital neutropenia	12 (6.7%)
Drug-related	12 (6.7%)
Vitamin B12 deficiency-related	5 (2.7%)
Other causes	8 (4.4%)
Celiac disease	2 (25%)
Tay-Sachs disease	2 (25%)
Glycogen storage disease type 1b	2 (25%)
IgA vasculitis (HSP)	2 (25%)

CMV: Cytomegalovirus, EBV: Epstein-Barr virüs, HSP: Henoch-Schönlein purpura.

(12.2%) are still being followed up. At the last follow-up, ANC was within normal limits in 69.4% (n=125) of the patients. Seventy-nine (63.2%) of these patients had post-infectious and 26 (20.8%) had with immune neutropenia.

Discussion

Neutrophils are produced from multipotent myeloid stem cells through granulopoiesis. They play a role in the immune response against mainly bacteria, and also contribute to the innate immunity.[1,7,8] Neutropenia is a common laboratory finding in children and also a common reason for referral to pediatric hematology units. Distinguishing between benign and severe pathological mechanisms of neutropenia is essential for protecting patients from infections, assessing their risk of malignant transformation, and guiding the implementation of appropriate supportive care and curative strategies.[1-5]

In clinical practice, neutropenia is usually grouped as mild, moderate, severe, and very severe, as in our study. It should be noted that this classification system is used in the non-infant period, since neutrophil normal values are different in the first year of life.[1,2] In addition to numerical grading of the depth of neutropenia, the age at which neutropenia arose and the underlying pathophysiology should be evaluated and thus diagnostic tests should be planned with this holistic approach.[4,6,9]

In the current study, the median age of all the patients enrolled in study was 4.8 years, whereas the median age of patients diagnosed with congenital neutropenia was 12 months. Consistent with the literature, congenital neutropenia cases are usually diagnosed in the early infancy period.[10] However, studies mentioning an older diagnostic age have also been reported.[5,7,11]

A family history of benign neutropenia may point to familial benign neutropenia. In addition, a consanguineous marriage may be a sign of congenital neutropenia or neutropenia due to a metabolic disorder.[12,13] Signs and symptoms on admission have a great value in directing the diagnostic process. Although a vast majority of pediatric patients presenting with neutropenia have transient and post-infectious neutropenia, a thorough patient and family history, along with a comprehensive physical examination, should be performed. In the present study, most of the patients had no complaints before and neutropenia was determined incidentally. Repetitive fever, oral-mucosal infections, unexpected skin lesions, recurrent pulmonary and serious infections that result in hospitalization are common signs for congenital neutropenias.[14] Similarly, in the present study, patients with congenital neutropenia were admitted with the signs and symptoms of serious infections.

Most of the underlying causes of neutropenia are acquired, benign, and transient. Congenital neutropenias and malignant etiologies are much less common.[6,9,14] In our study, similar to the literature, only 6.7% (n=12) of the patients were diagnosed with congenital neutropenia, whereas the remaining were diagnosed with secondary neutropenia, consisting of post-infectious, immune, drug-related, vitamin B12 deficiency and other rare causes of neutropenia. Furthermore, none of them were diagnosed with a malignancy. The findings of this study are consistent with the existing literature. It is important to emphasize that severe congenital neutropenia syndromes carry a significant risk of malignant transformation, with reported frequencies as high as 22%. Therefore, annual BMA should be undertaken in follow-up.[4,15-17] In patients with congenital neutropenia, maturation arrest of myeloid cells should be seen and dysplastic changes should be checked for myelodysplastic syndrome. Although not statistically proven, AMC and AEC were observed to be increased in congenital neutropenia patients regarding the enhanced phagocytic activity of these cell lines in the chronic decline of neutrophils. Anemia and thrombocytopenia were not observed in the majority of patients. Physical examination

findings such as lymphadenopathy, hepatomegaly, or splenomegaly were recorded in only a minority of cases, and none of the patients were diagnosed with hematologic malignancy. These findings suggest that in the absence of additional hematologic abnormalities or abnormal physical exam findings, neutropenia is more likely to be benign and transient.

As demonstrated in our study, infectious agents are the most common cause of transient neutropenia, typically presenting within the first week and resolving by the third week of illness. The mechanisms underlying post-infectious neutropenia are regarded as a decrease in production and an increase in demolition. This form of neutropenia is benign and frequently the agent is a virus, however, other bacterial or fungal agents can also develop neutropenia.[18,19] In our study, the most common cause of infections were viruses. The second most common cause was immune neutropenia. Although anti-neutrophil antibodies could not be assessed, the BMA of the patients were compatible with immune neutropenia, demonstrating an increased number of mature neutrophils. The clinical course of these patients were mild and reversible as reported in the literature.[20]

Regarding the other etiological causes, drug-related neutropenia was observed in 6.7% of our patients. The frequency is approximately 10% for childhood.[2,21] Almost all drugs can cause neutropenia, antimicrobials, anticonvulsants, antipsychotics and antipyretics being the most common ones. In our study, antiepileptics were responsible for 75% (n:9/12) of the cases. The primary mechanism is more complicated, consisting of both bone marrow toxicity and immune mediated mechanisms.[22,23] In general, these patients do not need any supportive care or treatment, owing to the resolution of neutropenia upon the withdrawal of the drug, similar to our study.[24,25]

Another important cause of neutropenia in childhood is nutritional deficiencies, especially vitamin B12, copper and folic acid deficiencies. The main mechanism is ineffective myelopoiesis and neutropenia alleviates after supplementation with the deficient nutrient.[2,26] Among our patients, 2.7% (n=5) had vitamin B12 deficiency-related neutropenia and their clinical course was benign. Also, there are several metabolic causes of neutropenia in childhood, including glycogen storage diseases, organic acidemias, and Shwachman-Diamond syndrome.[27,28] These conditions may require specialized management and follow-up due to their chronic nature and potential for severe complications, especially in regions where consanguineous marriage is frequent.

This study has several limitations. First, it was a retrospective single-center study, which may limit the generalizability of the findings to other populations or clinical settings. Second, anti-neutrophil antibody testing, which is important for confirming autoimmune neutropenia, could not be performed due to technical limitations. Third, although viral serologies were obtained in more than half of the patients, molecular diagnostic tests (such as PCR panels) were not routinely used, which may have led to underdiagnosis of certain viral etiologies. Additionally, the small number of patients with congenital neutropenia limited the ability to perform comprehensive statistical analyses or draw robust conclusions regarding this subgroup. Finally, long-term outcomes were not assessed beyond the average follow-up duration, which may have led to underestimation of late-onset complications or relapses.

In conclusion, this study highlights that pediatric neutropenia often does not require long-term follow-up by pediatric hematologists. One pivotal point to emphasize is that the patients in this cohort were referred at the time of first detection of neutropenia, and did not meet the definition of chronic neutropenia. As such, the findings of this study may not be directly applicable to patients with persistent neutropenia lasting longer than 3 months,

and should be interpreted within this context. Among the 180 patients, the majority had no significant underlying conditions, and 45% were incidentally diagnosed without any symptoms. The most common etiological cause was post-infectious neutropenia, accounting for 53.9% of cases. At the last follow-up, 69.4% of patients had normal ANC levels, and only 12.2% required ongoing follow-up. Importantly, congenital neutropenia patients had higher infection rates and required more intensive management. In infants younger than one year, the presence of recurrent mucocutaneous or organ-specific infections—particularly involving the gingiva, perianal region, or skin—together with laboratory findings such as severe neutropenia (ANC <500/mm^3), monocytosis, and eosinophilia, should raise suspicion for chronic neutropenia of congenital origin. Taken together, these findings suggest that pediatric neutropenia is often benign and self-limiting, particularly in cases related to transient or post-infectious causes. However, clinicians should maintain a high index of suspicion for inherited or persistent neutropenias, especially in infants presenting with recurrent infections, severe neutropenia, or abnormal leukocyte differentials. The identification of such clinical and laboratory predictors is critical for timely referral and management by pediatric hematologists.

Ethical approval

The study was approved by the Institutional Review Board of Dokuz Eylül University (approval number: 2022/04-04).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ŞA, HÖ; data collection: ŞA, ÖT; analysis and interpretation of results: ŞA, HÖ, ÖT, ŞY; draft manuscript preparation: ŞA, ÖT, ŞY. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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