Review Article

Diagnosis and Treatment Management in Patients with Autoimmune Neutropenia: A Review

Mohammadreza Saeidnia[1], Elnaz Vaziee[1], Amir Mahmoodzadeh[2], Masoumeh Abedini[3], Gholamhossein Tamaddon[4]*

1. Department of Hematology, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran.
2. Department of Clinical Biochemistry, Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran.
3. Department of Infectious Diseases, Kurdistan University of Medical Sciences, Sanandaj, Iran.
4. Diagnostic Laboratory Sciences and Technology Research Center, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran.

Received: April 25, 2019; Accepted: June 29, 2019

Abstract

Autoimmune neutropenia (AIN) is the frequent cause of neutropenia in infants and children. AIN is associated with a reduced neutrophil count, which is due to aberrant cell-mediated or humoral immune response. In this review, we will discuss the available diagnostic approaches and management of the diseases. We collected data from PubMed, Google Scholar, Medline, Web of Science databases, using a group of key words, such as neutropenia, autoimmune, diagnosis and management from 2000 until 2019. The most important aspects of primary assessment in the affected children were family history and physical examinations. Diagnostic methods in this disease are granulocyte indirect agglutination test (GAT) and granulocyte immunofluorescence test (GIFT). However, the sensitivity and specificity of these tests are low. In these patients, injection of granulocyte-colony stimulating factor (G-CSF), is the first line of treatment. Despite low prevalence, autoimmune neutropenia is a clinically significant disease and it is critical to identify it and pursue effective treatment in these patients.

Keywords: Autoimmune Neutropenia; Diagnosis; Treatment; Granulocyte-Colony Stimulating Factor, G-CSF;

***Corresponding Author:** Gholamhossein Tamaddon; **Email:** tamaddon.g@gmail.com
Please cite this article as: Saeidnia M, Vaziee E, Mahmoodzadeh A, Abedini M, Gholamhossein Tamaddon. Diagnosis and Treatment Management in Patients with Autoimmune Neutropenia: A Review. Arch Med Lab Sci. 2019;5(3):1-9. https://doi.org/10.22037/amls.v5i3.30970

Introduction

Overview of autoimmune neutropenia

Neutropenia is the reduction of absolute neutrophil count in the peripheral blood [1], and it is a relatively common blood disorder during childhood [2]. The normal range of neutrophils in peripheral blood depends on one's race and ethnicity and age. In Caucasian children who are one year old or more, neutropenia is defined as a neutrophil count of less than 1500 cell/μL. In infants who are less than one year old, 1000 cell/μL is considered the minimum normal count of neutrophil. Neutrophil count in peripheral blood of most Caucasians and Asians ranges from 1500 to 1700 cell/μL [1]. At least in 5% of the African people, their neutrophil count can be less than 1500 cell/μL, which is related to their Duffy negative blood group, also known as racial pseudo- neutropenia. When the neutrophils count is less than 500 cell/μL, neutropenia is considered as severe and clinically significant [3]. Neutropenia, like other reduced hematopoietic cell lines, can be researched in the sense of reduced production, increased circulatory marginalization, increased consumption, or destruction. Classification can be done based on ethiology. There are broad categories for neutropenia including infectious, drug-mediated, malignancy, congenital, and

autoimmune neutropenia. The cause of transient neutropenia can be related to viral infections, which lasts less than three months and occurs frequently. Autoimmune neutropenia is considered as a chronic disorder that lasts at least three months. In infants and children, the distinction between autoimmune neutropenia and benign chronic neutropenia is difficult and usually defined together. Many children who are diagnosed with chronic and idiopathic neutropenia are explained as secondary to autoimmune neutropenia. In most patients, the common feature of these conditions, is a benign course with good clinical characteristics. Unlike congenital neutropenia which is associated with reduced or loss of bone marrow production, patients with increased neutrophil destruction, such as autoimmune neutropenia have much lower rates of infection and mortality and rarely suffer from severe infections. During an acute infection, an appropriate augment in the neutrophil count can be helpful for diagnosis. Relatively mild, common childhood infections, such as upper respiratory tract infections, ear or skin infections might appear during the disease and in severe neutropenia, oral ulcers may also occur [4]. Autoimmune neutropenia is the most common childhood neutropenia [5]. The prevalence of this disease is 1 in 100,000 children per year [6, 7]. Since most children with this condition have a mild course, mostlikely a complete blood cell counts are never evaluated. Therefore, it seems the actual incidence of the disease is higher than the reported cases.

Autoimmune neutropenia in childhood occurs between 7-9 months and it is a common cause of neutropenia in children [8]. Generally, these disorders usually appear in the first two years of life [9]. On the whole, there is no clear relationship between the prevalence of autoimmune neutropenia and gender. A Japanese study of 18 patients reported that the age of onset is between 7 and 8 months of age [10]. But other data from a study on 157 patients revealed that most people experience the disease in the first 8 to 9 months of their life; however, disease diagnosis is confirmed after 3-4 months from the time of onset [5, 7]. The disease appears in all patients before the age of 5, and in 82% of the cases before 18 months. Three children developed the disease in the first three months of their life after alloimmune neutropenia diagnoses were ruled out. The disease spontaneously disappears in most 5-year-old children (more than 95%), lasting 18 to 24 months after the time of diagnosis [10, 11]. Children with autoimmune neutropenia who are older than 5 years are at higher risk for other immune or autoimmune diseases [1].

The main mechanism of this rare blood disorder is opsonization, in which neutrophils are destroyed by autoantibodies. This process accelerates the phagocytosis of antibody-coated neutrophils. Moreover, anti-neutrophil antibodies affect the function of target proteins and impair the function of neutrophils [12].

Autoimmune neutropenia is classified into primary and secondary. Primary immune-neutropenia is relatively common amongst infants and children and this condition is rather benign and self-limited [9]. Secondary immune-neutropenia is relatively common in adults and is associated with different pathological diseases including: infectious diseases, autoimmune diseases, hematological malignancies, transplantation, and drug-allergy [13]. Immune neutropenia in the neonatal period can be either alloimmune or autoimmune. Alloimmune neutropenia occures due to alloimmunization against neutrophil-specific antigens which do not appear on maternal white blood cells [11]. After the neonatal period, perhaps most children with autoimmune neutropenia have antibodies that are directed against neutrophil surface antigens. The outcome of neutropenia is the result of peripheral destruction of antibody-coated neutrophils. In the spleen of patients who are affected by autoimmune neutropenia, neutrophil phagocytosis was also detected [10]. The definite mechanism of autoantibody production is unknown. Most likely, antibodies that are produced against foreign antigens, such as viruses, have cross-reaction with self-antigens [14]. There is no specific viral antigen related to autoimmune neutropenia. For instance, a study of 240 sick infants and children found no significant association between autoimmune neutropenia and parvovirus B19 infection [4]. More than half of patients with autoimmune neutropenia have severe neutropenia. Leukopenia may also occur, but in more than half of the cases the total white blood cells count is normal, while monocytosis can also be present [7]. Most researches on the bone marrow of patients with primary autoimmune neutropenia have normal to increased cellularity, which indicates increased myloid to erythroid ratio without a reduction in mature granulocyte precursors [7, 15]. In a

study of 240 patients with certain autoimmune neutropenia, after assessing 133 bone marrow examinations, only 3% showed hypocellular bone marrow. In such cases, bone marrow examinations shows that antibodies bind to granulocyte precursors in addition to binding to mature neutrophils in the peripheral blood. This antibody-related destruction against fragmented neutrophils and the basic forms, might mimic the process of maturation arrest in the myelocyte and metamyelocyte stages [4].

Children with another immune cytopenia, such as immune- thrombocytopenia, autoimmune hemolytic anemia and chronic autoimmune neutropenia are more likely to have a secondary form, which is associated with other chronic diseases or immunological processes well past the age of 5 [11]. Secondary autoimmune neutropenia can appear at any age with different clinical courses. In older children and adolescents (more common in females) there is an increased association with other autoimmune diseases and less likelihood of self-remission [9]. Therefore, patients who develop autoimmune neutropenia after childhood, their disease lasts more than 3 years, and also, those with other congenital cell lineage abnormalities should be evaluated for secondary forms [16].

Diagnostic evaluation

When a child presents with neutropenia, the emphasis should be on determining the risk for infection and managing it. However, the definition of the main pathology plays an important role in estimating the chance of infection in childhood neutropenia. A complete medical history, physical examination, and family history can limit the differential diagnoses in the affected children. Usually, for a child with a history of autoimmune neutropenia, more laboratory tests and bone marrow examinations are not performed. In peripheral blood, anti-neutrophil antibodies can be helpful to diagnose autoimmune neutropenia. However, this test has limitations for diagnosis, due to its low sensitivity. Autoimmune neutropenia is common in the first two years of life and usually presents itself in apparently healthy children [17]. Usually, there is no specific physical examination for children with autoimmune neutropenia. However, there may be findings for mouth ulcers, ear infections, or upper respiratory tract infections [4, 18]. Generally, in these cases, unlike severe peripheral neutropenia, severe infections are not observed. Sometimes these children may also have a previous viral illness But showed no association between parvovirus infection and autoimmune neutropenia In children. [4]. At an early age, congenital factors and family history of neutropenia might be associated with recurrent fever and infections. A study by Fioredda et al. revealed that severe infectious side effects in autoimmune neutropenia were less common than in genetic neutropenia [19]. It is important to investigate the cause of neutropenia, since it can be helpful to predict the severity and guide both medical interventions and healthcare guidance for families. Secondary causes of autoimmune neutropenia are more common in children and adults [17]. Factors that contribute to secondary neutropenia include connective and autoimmune tissue diseases, medications, and malignancies [18]. The cause of secondary neutropenia is often multifactorial; anti- neutrophil antibodies, other mechanisms of neutrophil peripheral destruction , and the reduced granulopoiesis in the bone marrow might have roles in this type of neutropenia [20]. Splenomegaly and other physical findings, along with another cytopenia, should be considered in bone marrow examination to find the cause of malignancy and myelodysplasia [3]. Both Felty syndrome (including rheumatoid arthritis, splenomegaly, and neutropenia) and systemic lupus erythematosus are autoimmune diseases that are usually associated with neutropenia in adults. Nutropenia is well described for lupus erythematosus systemic disease. In a prospective study, 47% of patients with lupus-erythematosus were affected by systemic neutropenia [21]. This could be due to the similarity of neutrophil and Ro /SSA surface antigens in patients with systemic lupus erythematosus who have Ro/SSA antibodies [18]. Interestingly, anti-neutrophil antibodies have been identified in patients with systemic lupus erythematosus with or without the presence of neutropenia [22]. In Felty syndrome, neutropenia may be caused by immune complex, anti-neutrophile antibodies, which binds to neutrophil antigens and inflammatory cytokines (interferon-alpha, interferon-gamma), which can lead to neutrophil bone marrow production [18, 20]. In felty syndrome secondary autoimmune neutropenia can also be caused by large granular lymphocytic leukemia (LGL) which is a clonal malignancy of CD8+ T cells [18]. The common test for anti-neutrophil

antibodies has less usage in clinical procedures due to its low sensitivity and specificity [3].

Differential diagnosis in neutropenia

Cyclic neutropenia

Cyclic neutropenia is a rare autosomal recessive disorder, caused by mutations in the neutrophil elastase gene. It seems the mutation in this enzyme accelerate myeloid cell death; however, the definite mechanism of cyclic neutropenia is not completely defined [17]. These patients usually present severe neutropenia at the site of the oral ulcer and bacterial infection. Bone marrow examination shows normal hematopoiesis and times of myelocytic maturation arrest in predictable intervals. These periods of neutropenia often occur in 21-day intervals and show severe neutropenia for 3-5 days, with a rapid reduction in the count of neutrophils to more than 1.5×10^9 cells/L [17, 23]. When the count of neutrophils is the lowest in the peripheral blood, patients usually suffer from stomatitis, abscesses, and severe infections [17]. Due to its cyclic nature, diagnosis can be confusing and it requires a continuous blood cell count, which must be performed 3 times a week for six weeks to record the neutropenia cycles regularly [17, 23].

Severe Congenital Neutropenia

Severe congenital neutropenia, also known as Castleman disease, is a rare and heterogeneous group of diseases that is often associated with severe neutropenia and life-threatening infections in early childhood [9]. Severe neutropenia is stable, and patients with this disease experience deep tissue infections, pneumonia, and severe sepsis. Genetic mutations, such as elastase and HAX1 mutations were observed in patients with severe congenital neutropenia [17]. These patients may also experience dysmorphic features and metabolic disorders [9, 17, and 24]. Usually, bone marrow shows a maturation arrest during the promyelocyte phase [9]. About 20-30 percent of these patients are at risk of leukemia and myelodysplastic syndrome [17, 25]. Other bone marrow failure syndromes should also be considered for severe infections, chronic neutropenia, or other clinical and laboratory findings.

Neutropenia associated with drug administration and nutrient deficiencies

Antiepileptic and antibiotics are the most common non-chemotherapeutic drugs, leading to drug agranulocytosis. The definite mechanism of neutropenia is unknown, but findings in anti-neutrophil antibodies in some patients show immune processes [26]. Onset after exposure can be variable and it may take 1 week to 1 month after removing the effective agent for the cell count to become normal. Vitamin B12, folate, or copper deficiency is also considered as a cause of neutropenia and this condition is resolved when these nutrients have been replaced [9].

Autoimmune neutropenia associated with other autoimmune diseases

Evans syndrome, autoimmune hemolytic anemia, and immune thrombocytopenic purpura are the most common diseases associated with neutropenia in children. Systemic lupus erythematosus and other autoimmune disorders were reported in patients [9]. Usually, children with secondary autoimmune diseases are older and female. Since it may be difficult to distinguish at primary manifestations, a study suggested that detecting anti-neutrophil antibodies may help differentiate between primary and secondary autoimmune neutropenia. This is because antibodies specific to HNA-1a and HNA-1b are found in patients with primary autoimmune neutropenia and pan-FcgRIIIb in secondary autoimmune neutropenia [14].

History and findings during physical examination are the most important aspects of the initial assessment of a child with neutropenia. If a review of the child's personal and family history does not help, and the physical examination is normal, autoimmune neutropenia is possible; hence, laboratory evaluation is recommended. A complete blood cell count and peripheral blood smear evaluation are necessary to prove neutropenia and to rule out another cytopenia. Also, morphological abnormalities should be performed in all cases.

Assessment of anti-neutrophilic antibodies can be helpful. However, as mentioned, its sensitivity and specificity are low for diagnosing autoimmune neutropenia. For people with a history of severe infections, growth abnormalities, or other unusual features, further evaluations are essential. There is no need for bone marrow examination for classic autoimmune neutropenia, but if production defect is presumable, this examination can be helpful.

Anti-neutrophil antibody detection methods

For the first time in 1975, Boxer et al. detected antineutrophil antibodies, which accelerated the destruction of neutrophils. This process was induced by the reticuloendothelial system in three out of five hospitalized patients [20, 27]. In 1986, this finding was confirmed by Hadley et al., and reported a rise in antigranulocytes opsonic activity in half of the patients with neutropenia, which indicates an immunological cause [28]. Previously, animal studies showed that anti-neutrophil antibodies could lead to neutropenia by similar mechanisms of opsonization and increased phagocytosis [29].

However, case studies of patients with autoimmune neutropenia reported different levels of anti-neutrophil antibodies in suspected patients with autoimmune neutropenia. This may be due to the antibody titer lower than the detectable limit. Besides, the association between autoantibody levels and the severity of neutropenia was observed in patients who were suspected of autoimmune neutropenia [20].

At least two tests are necessary to diagnose anti-neutrophil antibodies, including an indirect granulocyte agglutination test (GAT) and granulocyte immunofluorescence test (GIFT) [30]. However, each of these tests has its limitations. Indirect granulocyte agglutination test can show false-positive results, since neutrophils may agglutinate spontaneously [20, 31]. However, this test can detect aggregated antibodies, such as anti-HNA-3a [32]. Granulocyte immunofluorescence test uses fluorescent anti-human neutrophil antibodies to detect anti-neutrophil antibodies. However, the granulocyte indirect immunofluorescence test exposes the patient's serum to control neutrophils and autoantibodies are identified, using fluorescent anti-immunoglobulin antibodies. Evaluation of monoclonal antibody-specific immobilization of granulocyte antigen (MAIGA) can overcome the false-positive results since specific monoclonal antibodies bind to neutrophil gene antigens that are adherent to human antibodies [20, 31]. However, this assessment is usually unavailable and it usually cannot detect the anti-HNA-3a antibodies, which plays the most important role in TRALI reactions. Recently, a flow cytometric white blood cell immunofluorescence test (Flow-WIFT) was performed to detect these antibodies. Recent studies showed that this test can detect more granulocyte reactive antibodies than the immunofluorescence granulocyte test, suggesting this test as a screening test in the future [32].

Table 1. General Diagnostic Methods for Childhood Neutropenia [35]

Complete Blood Count (CBC)
Absolute Neutrophil Count(ANC)
Bone marrow examination to evaluate maturation or maturation arrest in myeloid, megakaryocytes and erythroid series
Performing FISH and karyotype tests on bone marrow samples to assess myelodysplastic risk (MDS), especially for chromosomal abnormalities 5 and 7
Electronic microscopic examination
anti-neutrophil antibodies detection ✓ **Granulocyte Immunofluorescence Test(GIFT)** ✓ **Granulocyte Indirect Immunofluorescence Test (GIIFT)** ✓ **Granulocyte Aggregation Test (GAT)** ✓ **ELISA test** ✓ **Monoclonal Antibody Immobilization of Granulocyte Antigens (MAIGA)**
Immunological tests ✓ **Immunoglobulin measurement(IgA, IgM, IgG, IgE)** ✓ **Cell immunity evaluation(proliferation of T-lymphocytes and its subsets, counting and functional evaluation of NK cell)** ✓ **Anti-nuclear antibodies(C3, C4, CH50)**
Screening of metabolic diseases ✓ **Amino acids screening in plasma and urine** ✓ **Vitamin B12 , folic acid and copper levels in serum**
Pancreatic disease findings ✓ **Trypsinogen and iso-amylase level in serum**
Chromosome breakage test(for diagnosing Fanconi anemia)
Serum Muramidase level(for assessing inefficient production of myeloid series)
Evaluation of CD55, CD59 factors with flow cytometry test for diagnosing PNH disease.
Measuring Bone Density(14% of patients with neutropenia present osteoporosis and low bone density)
Evaluation of genetic mutation (ELA2, HAX1, LYST GFI-1, WAS), Shwachman–Diamond syndrome

Table 2. differential diagnosis for Childhood Neutropenia [9]

	Infection	Splenomegaly Hepatomegaly	Growth Retardation	Anemia/Low Platelets	General Aspects
Autoimmune Neutropenia	Mild	No	No	No	Occasional diagnosis by age
Leukemia	_	Yes	No	Yes	Lactate dehydrogenase ↑
Secondary Autoimmune Neutropenia	Mild/Moderate	Sometimes	No	Probably yes	Another autoimmunity
Shwachman–Diamond Syndrome	Mild/Moderate	Yes	Yes	Frequently	Pancreatic failure
Glycogen Storage Disease type 1	Moderate	Hepatomegaly	Yes	No	Hypoglycemia Ketoacidosis
Pierson Syndrome	Severe	Probably occurs Hepatomegaly	Yes	Yes	Lactic acidosis ↑
Severe Congenital Neutropenia	Severe	No	Occasionally	No	Indigestion/Anomalies
Cyclic Neutropenia	Severe	No	No	No	Mouth ulcers
Neutropenia after Infection	_	Probably yes	No	Probably mild	Medical history
Drug-Mediated Neutropenia	Moderate/Severe	No	No	No	Medical history

Autoimmune neutropenia treatment

Usually, primary autoimmune neutropenia is self-limited in children and due to the storage of mature neutrophils, severe infections are very rare in the bone marrow. There is no agreement on the procedure of fever examination in children with classic autoimmune neutropenia. Multiple therapies such as corticosteroids, intravenous immunoglobulin, and granulocyte-stimulating factor (G-CSF) have been tested and reported in articles, but only G-CSF has been effective in increasing neutrophil counts [18]. Rituximab, which is a monoclonal antibody against CD20, has been used to treat patients with autoimmune neutropenia, but has shown little efficacy [33]. Recombinant human granulocyte-colony stimulating factor (G-CSF) stimulates demargination of neutrophils from tissue and reduces neutrophil apoptosis [18]. This factor is effective in increasing the absolute counts of neutrophil to more than 1×10^9 cells/L and can prevent infection. In patients with cyclic neutropenia and severe congenital neutropenia, fatal bacterial infections were observed; hence, G-CSF therapy is suggested [17].

In 2011, "Associazione Italiana di Emato-Oncologia Pediatrica (AIEOP)" joined a group of international experts to decide for autoimmune neutropenia treatments infections, surgery, or timely follow up. The GCSF dose depends on the disease condition and the target autoimmune neutropenia range, which was set between 1.0×10^9 cells/L and 5.0×10^9 cells/L. In limited cases of infection in autoimmune neutropenia, a starting dose was recommended 1 to 2 µg/kg/day for one week. If the absolute neutrophil count in peripheral blood remains lower than 1.0×10^9 cells/L, increasing 1 to 2 µg every 5-7 days is justifiable [34].

In general, patients with autoimmune neutropenia respond quickly and strongly to G-CSF therapy due to adequate bone marrow supplies. However, treatment with G-CSF (especially high doses) can cause significant bone pain [3]. To evaluate neutropenia, experts have recommended monthly follow up. If neutropenia continues, a re-performing test for indirect anti-neutrophil antibodies is recommended. Remarkably, the daily use of prophylactic antibiotics is not recommended for patients with autoimmune neutropenia [34]. Generally, the use of

prophylactic antibiotics including cotrimoxazole is not recommended for classic autoimmune neutropenia and is usually administrated for patients with mild recurrent infections and other disorders. As mentioned previously, in a retrospective study on 240 infants with primary autoimmune neutropenia, 90% had mild infections. Although they suffered from severe peripheral neutropenia, recovered with systemic antibiotics [4].

In total, 89% of these patients received prophylaxis with cotrimoxazole, and prophylaxis was administrated only after recurrent infections. Fioredda and colleagues reported infection in 40% of patients with autoimmune neutropenia, who mainly suffered from skin and soft tissue infections [19].

Conclusion

Autoimmune neutropenia is caused by autoantibodies that are produced against neutrophil membrane proteins, leading to increased peripheral clearance. Although neutropenia is shown as a severe peripheral neutropenia, the bone marrow storage and response to bacterial infection is generally normal. The clinical course of autoimmune neutropenia is usually mild and often resolves within 1 to 3 years. Diagnosis remains clinical, since it is difficult to detect neutrophil antibodies using the current methods. Even in agglutination and immunofluorescence combination tests, the identification of neutrophil surface antigens is being developed and will provide a bright future into the pathophysiology of immune neutropenia. Common therapy including prophylactic antibiotics or G-CSF is generally not recommended and may be used individually for those patients with recurrent infections or other clinical manifestations. Although autoimmune neutropenia does not usually require vigorous medical intervention, the patients should be regularly monitored, until the condition resolves, and the patient recovers fully. Monitoring schedules into the patient's condition including every 1-3 months complete blood cell counts evaluation and annual bone marrow aspiration examination should be performed regularly.

Conflicts of Interest

The authors declared no conflict of interests.

Acknowledgments

Authors appreciation all the people who helped us in this research at Shiraz University of Medical Science (Tehran, Iran).

References

1. Newburger PE, Dale DC, editors. Evaluation and management of patients with isolated neutropenia. Seminars in hematology; 2013: Elsevier.

2. Dinauer M. The phagocyte system and disorders of granulopoiesis and granulocyte function. Nathan and Oski's hematology of infancy and childhood. 1998:889-967.

3. Newburger PE. Autoimmune and other acquired neutropenias. Hematology 2014, the American Society of Hematology Education Program Book. 2016; 2016(1):38-42.

4. Bux J, Behrens G, Jaeger G, Welte K. Diagnosis and clinical course of autoimmune neutropenia in infancy: analysis of 240 cases. Blood, The Journal of the American Society of Hematology. 1998;91(1):181-6.

5. Bruin M, Dassen A, Pajkrt D, Buddelmeyer L, Kuijpers T, De Haas M. Primary autoimmune neutropenia in children: a study of neutrophil antibodies and clinical course. Vox sanguinis. 2005; 88(1):52-9.

6. Lyall E, Lucas G, Eden O. Autoimmune neutropenia of infancy. Journal of clinical pathology. 1992; 45(5):431-4.

7. Farruggia P, Fioredda F, Puccio G, Porretti L, Lanza T, Ramenghi U, et al. Autoimmune neutropenia of infancy: Data from the I talian neutropenia registry. American journal of hematology. 2015; 90(12):E221-E2.

8. Wang LY, Wang CL, Chu CC, Lee HL, Ho HT, Liang DC, et al. Primary autoimmune neutropenia in children in Taiwan. Transfusion. 2009; 49(5):1003-6.

9. Farruggia P, Dufour C. Diagnosis and management of primary autoimmune neutropenia in children: insights for clinicians. Therapeutic advances in hematology. 2015;6(1):15-24.

10. Taniuchi S, Masuda M, Hasui M, Tsuji S, Takahashi H, Kobayashi Y. Differential diagnosis and clinical course of autoimmune neutropenia in infancy: comparison with congenital neutropenia. Acta Paediatrica. 2002; 91(11):1179-82.

11. Teachey DT, Lambert MP. Diagnosis and management of autoimmune cytopenias in childhood. Pediatric Clinics. 2013; 60(6):1489-511.

12. Shastri KA, Logue GL. Autoimmune neutropenia [see comments]. 1993.

13. Sebastian S, Ashton K, Houston Y, Diggory TM, Dore P. Anti-TNF therapy induced immune neutropenia in Crohns disease-report of 2 cases and review of literature. Journal of Crohn's and Colitis. 2012;6(6):713-6.

14. Bruin MC, von dem Borne AEK, Tamminga RY, Kleijer M, Buddelmeijer L, de Haas M. Neutrophil antibody specificity in different types of childhood autoimmune neutropenia. Blood, The Journal of the American Society of Hematology. 1999; 94(5):1797-802.

15. Bussel JB, Abboud MR. Autoimmune neutropenia of childhood. Critical reviews in oncology/hematology. 1987;7(1):37-51.

16. Dufour C, Miano M, Fioredda F. Old and new faces of neutropenia in children. Haematologica. 2016; 101(7):789.

17. Dale DC. How I manage children with neutropenia. British journal of haematology. 2017; 178(3):351-63.

18. Afzal W, Owlia MB, Hasni S, Newman KA. Autoimmune Neutropenia Updates: Etiology, Pathology, and Treatment. Southern medical journal. 2017; 110(4):300-7.

19. Fioredda F, Calvillo M, Burlando O, Riccardi F, Caviglia I, Tucci F, et al. Infectious complications in children with severe congenital, autoimmune or idiopathic neutropenia: a retrospective study from the Italian Neutropenia Registry. The Pediatric infectious disease journal. 2013; 32(4):410-2.

20. Capsoni F, Sarzi-Puttini P, Zanella A. Primary and secondary autoimmune neutropenia. Arthritis research & therapy. 2005;7(5):208.

21. Nossent J, Swaak A. Prevalence and significance of haematological abnormalities in patients with systemic lupus erythematosus. QJM: An International Journal of Medicine. 1991; 80(1):605-12.

22. Starkebaum G, Arend W. Neutrophil-binding immunoglobulin G in systemic lupus erythematosus. The Journal of clinical investigation. 1979; 64(4):902-12.

23. Dale DC, Welte K. Cyclic and chronic neutropenia. Hematopoietic Growth Factors in Oncology: Springer; 2010. p. 97-108.

24. Stroncek D. Granulocyte gene polymorphisms and mutations: effects on immune response and neutrophil proliferation. Vox sanguinis. 2004; 87:101-4.

25. Rosenberg PS, Zeidler C, Bolyard AA, Alter BP, Bonilla MA, Boxer LA, et al. Stable long-term risk of leukaemia in patients with severe congenital neutropenia maintained on G-CSF therapy. British journal of haematology. 2010; 150(2):196-9.

26. Andrès E, Zimmer J, Affenberger S, Federici L, and Alt M, Maloisel F. Idiosyncratic drug-induced agranulocytosis: Update of an old disorder. European journal of internal medicine. 2006; 17(8):529-35.

27. Boxer LA, Greenberg MS, Boxer GJ, Stossel TP. Autoimmune neutropenia. New England Journal of Medicine. 1975; 293(15):748-53.

28. Hadley AG, Holburn A, Bunch C, Chapel H. Anti-granulocyte opsonic activity and autoimmune neutropenia. British journal of haematology. 1986; 63(3):581-9.

29. Simpson DM, Ross R. Effects of heterologous antineutrophil serum in guinea pigs: Hematologic and ultrastructural observations. The American journal of pathology. 1971; 65(1):79.

30. Bux J, Chapman J. Report on the second international granulocyte serology workshop. Transfusion. 1997; 37(9):977-83.

31. Farruggia P. Immune neutropenias of infancy and childhood. World Journal of Pediatrics. 2016; 12(2):142-8.

32. Heinzl M, Schönbacher M, Dauber EM, Panzer S, Mayr W, Körmöczi G. Detection of granulocyte-reactive antibodies: a comparison of different methods. Vox sanguinis. 2015; 108(3):287-93.

33. Dungarwalla M, Marsh J, Tooze J, Lucas G, Ouwehand W, Pettengell R, et al. Lack of clinical efficacy of rituximab in the treatment of autoimmune neutropenia and pure red cell aplasia: implications for their pathophysiology. Annals of hematology. 2007; 86(3):191-7.

34. Fioredda F, Calvillo M, Bonanomi S, Coliva T, Tucci F, Farruggia P, et al. Congenital and acquired neutropenias consensus guidelines on therapy and follow-up in childhood from the Neutropenia Committee of the Marrow Failure Syndrome Group of the AIEOP (Associazione Italiana Emato-Oncologia Pediatrica). American journal of hematology. 2012; 87(2):238-43.

35. Celkan T, Koç BŞ. Approach to the patient with neutropenia in childhood. Turkish Archives of Pediatrics/Türk Pediatri Arşivi. 2015;50(3):136.