

## STEPS IN DIAGNOSIS OF CHRONIC IDIOPATHIC NEUTROPENIA: IS IT THE TIME FOR SERBIAN PATIENT REGISTRY?

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Chronic neutropenia (CN) corresponds with absolute count of neutrophils below  $1.8 \times 10^9/L$  in last three months. Besides, neutropenia that persists more than three months and in absence of underlying diseases, chemical components, irradiation, use of particular drugs, inflammation, is defined as chronic idiopathic neutropenia (CIN). There are three types of CN - severe, moderate and mild, with or without extra-hematopoietic manifestations. The aim of this report was to define a stratified approach toward patient with hypothesis of CIN, including timely patient recognition with consequent follow-up and actions afterwards based on recommendation from EuNet INNOCHRON- European Network for Innovative Diagnosis and Treatment of Chronic Neutropenias. Case presented a 40-year-old female who went to the Hematology Department of the University Clinical Center Niš for regular health condition and blood count control. Since she was 21, she has been monitoring neutropenia, which occurred immediately after first child birth. Laboratory parameters and peripheral blood smear values were within physiological range. Performed immune assays excluded the immune background of neutropenia. In the next step, we excluded viral infections as a cause of neutropenia with particular serological tests. Also, a bone marrow aspiration was performed with results in physiological range.

Chronic neutropenia can be associated with serious health complications. The Severe Chronic Neutropenia International Registry (SCNIR) is a global organization dedicated to finding the causes, consequences and best treatments for severe CN. Similar to other European countries, we suggest the introduction of defined approach to diagnosis, registration and monitoring of chronic neutropenia patients in Serbia through Register.

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### Introduction

Chronic neutropenia (CN) is defined as reduced absolute neutrophil count below  $1.8 \times 10^9/L$  during three or more months. These latter cate-

gories of CN, include benign and uncomplicated forms of the disease but also pre-myeloid dysplastic syndrome cases, associated or not with clonal hematopoiesis (1). In addition, if low count of neutrophils persisted in absence of underlying diseases, chemical components, irradiation, use of drugs, infectious disease, inflammation, autoimmune diseases and malignancies, neutropenia can be defined as chronic idiopathic neutropenia (CIN) (1, 2).

In clinical practice there are patients with long lasting neutropenia, without any related health problems or serious life-threatening conditions. In addition, CIN can express extra-hematological symptoms, depending on the severity of neutropenia and characteristics of patients (2, 3).

Moderate to severe bacterial infections are common in patients with CN (3). However, infections are more common in patients with severe CIN when the absolute neutrophils count is less than  $0.5 \times 10^9/L$ . In that case, this hematological disease is often accompanied with extra-hematological disorders, fever, chronic inflammation of the oropharynx as well as severe infections (4, 5).

The treatment of patients with CNP depends on the type and severity of the underlying disease. There is currently no specific therapy for severe CN, but mostly patients are treated symptomatically. The approach towards patients may consist of a simple follow-up of uncomplicated cases, but also it may require the administration of granulocyte colony stimulating factor (G-CSF), antimicrobial and immunomodulatory agents, or haemopoietic stem cell (HSC) transplantation or even experimental gene-based interventions using CRISPR-Cas9 technology (5). More recently, G-CSF has been used in therapy to accelerate the growth and maturation of myeloid cells, especially neutrophils (5, 6).

An idea of registration of CIN patients and systematization of their data is realized in numerous European countries (Italy, Greece, France, etc). The registry is required form for adequate collection and analysis of clinical data, comparison in relation to geographical, ethnic, and social characteristics, diagnosis and treatment of all patients with CN. Therefore, an adequate approach to those patients can be achieved through introduction of worldwide registry of CN patients. The Severe Chronic Neutropenia International Registry (SCNIR) is a global organization dedicated to finding the causes, consequences and best treatments for severe CN. The SCNIR opened in 1994 after researchers discovered that the hematopoietic growth factor called granulocyte colony stimulating factor (G-CSF) is an effective treatment for these patients.

Regarding the needs of clinicians and patients, central collecting of data in National Registry has to be established in our country too. It is a great challenge to introduce and implement in clinical practice an adequate Registry suitable for the use by physicians. The establishment of the registry of CN patients in Serbia could help and facilitate the monitoring, diagnosis and treatment (1, 5).

Therefore, we presented a case which included steps in an approach towards diagnosis of CIN in one patient. Hence, the aim was to define a stratified approach towards CIN, including timely patient recognition with consequent follow-up and actions afterwards. Also, the case report represented the importance of introduction registry data regarding optimal monitoring and risk management in CN.

### Case report

A 40-year-old female patient attended the Hematology Clinic, University Clinical Center Niš for regular monitoring of health condition and blood count control. Since she was 21, she has been following up neutropenia, which occurred immediately after giving birth for the first time. After a detailed anamnesis, we determined that the patient did not have a positive family history and comorbidities, except anemia, which persisted from first child birth, too.

The latest results of the patient's blood analysis showed the presence of neutropenia which was

similar to the earlier control. The neutrophils count was low during the previous years.

In the latest visit, laboratory parameters showed:

- white blood count  $2.2 \times 10^9/L$  ( $3.9-10 \times 10^9/L$ ),
- neutrophils  $1.2 \times 10^9/L$  ( $1.6-7 \times 10^9/L$ ),
- eosinophil  $0.1 \times 10^9/L$  ( $0.1 - 0.6 \times 10^9/L$ ),
- lymphocytes  $0.8 \times 10^9/L$  ( $0.8-5 \times 10^9/L$ ),
- monocytes  $0.1 \times 10^9/L$  ( $0.1-1 \times 10^9/L$ ),
- basophils  $0 \times 10^9/L$  ( $0-0.2 \times 10^9/L$ ),
- red blood count ( $5.13 \times 10^{12}/L$ ),
- hemoglobin (111 g/L),
- hematocrit (0.367 L/L),
- platelets ( $176 \times 10^9/L$ )

were in physiological range.

As a second step, a peripheral blood smear was performed, whereas cells did not show any pathological changes. Further, we run immune analysis, serum immunoglobulin levels and ANA and Anti DNA screen aimed to exclude the immune background of neutrophils account disorder. Results were within the reference values:

- IgG 9.03 g/L (7.0 - 16 g/L),
- IgA 0.95 g/L (0.7 - 4 g/L),
- IgM 1.97 g/L (0.4 - 2.3g/L),
- anti dsDNK 6.2 (< 25),
- ANA 0.1 (< 1).

Direct and indirect COOMBS tests gave negative results too. Biochemical status of patient showed normal range of all biochemical parameters, although iron was low:

- serum glucose 5.7 mmol/L,
- urea 4.0 mmol/L,
- creatinine 73.7 mmol/L,
- total bilirubin 8.2  $\mu\text{mol/L}$ ,
- total bilirubin 1.5  $\mu\text{mol/L}$ ,
- total proteins 66.4 g/L,
- albumins 44 g/L,
- AST 15 U/L,
- ALT 15 U/L,
- folate 13.6 ng/mL,
- vitamin B12 522 pmol/L,
- hTSH 1.4188 mU/L.

In order to exclude viral infections as a cause of neutropenia, serological tests were performed, but the results were negative (HBs Ag, HCV Ag, CMV Ag, EBV Ag, Parvovirus, and HIV Ag).

A bone marrow aspiration was performed to remove the suspicion of a malignancy or other hematological disease presented with a decreased number of neutrophils. The results were as follows: myeloblast 0%, promyelocytes 6%, myelocytes 4%, neutrophil granulocytes 10%, metamyelocytes 9%, no segments granulocytes 3%, segments granulocytes 25%, eosinophil granulocytes 2%, basophil granulocytes 2%, monocytes 6%, lymphocytes 14%, normoblasts 19%.

The final step was the analysis of dietary habits. Nevertheless, malnutrition was not present (BMI was 25 kg/m<sup>2</sup>) and hypoalbuminemia as well, but the analysis showed lack of proteins, particularly from red meat and sufficient carbohydrates.

## Discussion

The diagnosis of CIN has to be made on the basis of the absolute number of neutrophils and the exclusion of other underlying diseases. Also, there is a need to collect as more information as you can, regarding family history, medical treatments, drugs, health status of patients. Nowadays the greatest challenge is to timely provide useful "point of care" information to clinicians and patients (5). The possibility of congenital neutropenia in an adult patient should be kept in mind whenever a patient presents with a life-long history of (severe) neutropenia even in the absence of infection, also if it has characteristic recurrent oral lesions and periodontal disease or features of organ malformation.

Frequently, the base of congenital neutropenia is disorders of neutrophil production associated with mutations in more than 20 recognized genes and more still unknown genetic aberrations. Since the results of these genetic changes are impaired neutrophil differentiation and/or survival, varying degree of propensity to malignancy and frequent extra hematopoietic disorders (1, 6). In addition, ethnic variations in genetic polymorphisms may lead to lower number of neutrophils.

On the other hand, acquired CNP encompass diverse disease entities which are based on unknown pathogenic mechanisms or cellular immune processes of antibodies against neutrophils. With or without clonal hematopoiesis, every CN has to be timely recognized and requires close monitoring aimed at avoiding complications.

Severe CIN is a very rare disease that occurs without a known and clear cause, rather in adults than pediatric population, mostly in women. Very little is still known about its nature.

Studies showed that mutations on the ELANE gene showed changes on HAKS1, GFI1, WAS, CSF3R or G6PC3 genes especially related to severe neutropenia (7, 8). Most of *de novo* mutations and transmission can be autosomal dominant, recessive or X-linked. In previous studies, there is a strong evidence of the frequency of those mutations, and their dependence on the ethnicity of the patients (8, 9). Furthermore, a mutation in the JAGN1 gene has been identified in some patients, which disrupts further signaling at G-CSF receptors and explains the non-response to therapy with recombinant human G-CSF (10).

In adults, the use of particular drugs can cause the adverse effects and decreased count of neutrophils (anti-infectives, antipsychotics, anti-thyroids drugs) (11-13).

The variety of causes and symptoms of neutropenia makes diagnosis, monitoring and treatment of patients very difficult. For each follow-up, it is necessary to take a good anamnesis with detailed patient data, hematological, clinical data, medication list and other relevant medical and non-medical information. According to recommendation, detailed anamnesis was taken in the reported case. Our patient did not show any possibility of low neutrophil level explanation.

In addition, it is known that chronic or acute viral infections such as hepatitis, HIV, cytomega-

lovirus (CMV) or influenza may be associated with neutropenia. The performed tests in our case were negative, so we excluded virus-induced neutropenia.

Further, our patient had a healthy bone marrow aspiration finding. Since the bone marrow aspiration is currently without a pathological substrate, we plan to further monitor the patient in terms of periodic testing of blood smears.

The defined stepped approach includes investigation of autoimmune base on neutropenia. Regarding this step we performed immunological tests and excluded autoimmune disease. Testing of anti-neutrophil antibodies is performed more frequently in the pediatric population of patients, while in adults this type of testing is not very useful. In adults, an increased level of polyclonal gamma globulins supports the diagnosis of autoimmune neutropenia (14, 15).

As a final step we collected dietary habits data. Previous studies showed a high prevalence of anemia and neutropenia in a population of young American and Northern European patients with anorexia. Hematological abnormalities in patients with anorexia or diet were strictly related to the duration of the diseases, in particular CN (16). There are numerous studies on hematological disorders in anorexia or protein-deficient diet that prove an increased prevalence of anemia, leukopenia and thrombocytopenia. Lambert et al. explained the relationship between the index of total body fat mass and bone marrow consumption and the lower number of erythrocytes, leukocytes, neutrophils and platelets (17).

Caloric malnutrition also may lead to neutropenia, but it is usually mild. In addition, patients with folate or vitamin B12 deficiency can be exposed to low neutrophils number, too. For that reason, we control levels of vitamin B12 and folate in serum, and investigate dietary habits. Low calorie diet not only decreases the reserve of leukocytes in bone marrow but also leads to degeneration of leucocytes during their transition from BM to peripheral blood (18, 19).

In patients undergoing neutropenia treatment decisions should be patient-centered and based on the clinical presentation of the disease (20, 21). Results show an association between neutropenia and level of leptin and adiponectin. Leptin is a hormone that regulates nutrition and is produced from adipocytes (22). Leptin acts as a signaling molecule that transmits energy from food to the immune and neuroendocrine systems. Children with congenital leptin deficiency have reduced lymphocyte numbers and show an increased risk for infections and death caused by infection in childhood (23). We hypothesized a possible association between the type of diet and changes in adipokines, and will focus on intensive monitoring of diet-related behaviors and related biochemical monitoring.

Aimed to find link between leptin, adiponectin and number of neutrophils, our next step will include quantification of serum leptin in patients with CIN. Also, we are planning genetic screening of patients which may help to illumination of neutropenia.

Creating the registry of patients with neutropenia is a big challenge for many reasons, particularly for better approach, risk control and achieving optimal health outcomes. There are already high-quality registries for neutropenia in Europe (24). The SCNIR is a voluntary organization, with over than 25 years of existence, supported primarily by government grants and private gifts. Participation benefits patients, their families and their physicians by providing up-to-date information about severe CN and its treatment options.

It is important to introduce this registry in Serbia similar to other countries. The registry data would help physicians in diagnosis, monitoring and treatment of patients with neutropenia.

The prognosis of patients with CNP is closely correlated to the underlying pathogenesis, the degree of neutropenia and the propensity for leukemic transformation. Accurate diagnosis is mandatory to avoid omissions and risk stratification as well as treatment choice. Hence, we can suggest to

establish the register of chronic neutropenia patients in Serbia. (20, 24, 25).

### **Conclusion**

Based on the results of performed examinations and analyses, we assumed chronic idiopathic neutropenia in our patients. The stepped approach gives to hematologists an opportunity to make right choice in monitoring and treatment. The registry of this and similar cases may provide their comparison and consequently better understanding, timely diagnosis and treatment of CNI.

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## Prikaz bolesnika

UDC: 616.15-073  
doi:10.5633/amm.2022.0112**STEPENOVANI DIJAGNOSTIČKI POSTUPAK ZA HRONIČNU NEUTROPENIJU: DA LI JE VREME ZA REGISTAR U SRBIJI?***Sanja Veličković<sup>1,2</sup>, Miodrag Vučić<sup>1,2</sup>, Nikola Stefanović<sup>1</sup>, Filip Veličković<sup>3</sup>, Eirini Mauroudi<sup>4,5</sup>, Helen A. Papadaki<sup>4,5</sup>, Aleksandra Catić Đorđević<sup>1</sup>*<sup>1</sup>Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija<sup>2</sup>Univerzitetski klinički centar Niš, Klinika za hematologiju i kliničku imunologiju, Niš, Srbija<sup>3</sup>Univerzitetski klinički centar Niš, Centar za nuklearnu medicinu, Niš, Srbija<sup>4</sup>Univerzitet na Kritu, Medicinski fakultet, Laboratorija za istraživanje hemopoeze, Heraklion, Grčka<sup>5</sup>Univerzitetska bolnica Heraklion, Departman za hematologiju, Iraklion, Grčka

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Hronična neutropenija javlja se kada, minimum, tri meseca broj neutrofila bude ispod  $1,8 \times 10^9/L$ . Ukoliko neutropenija perzistira duže od tri meseca, bez prisutne druge bolesti, izlaganja hemijskim supstancama, zračenju, infekcijama, inflamacijama, različitim lekovima, koji mogu da uslove nastanak neutropenije, onda govorimo o hroničnoj idiopatskoj neutropeniji. Prema težini, razlikujemo ozbiljne, umereno ozbiljne i blage neutropenije, koje mogu biti sa ekstrahematološkim manifestacijama ili bez njih.

Cilj ovog rada je da prezentuje definisani stepenovani pristup kod bolesnika sa pretpostavljenom dijagnozom hronične neutropenije, uključujući pravovremeno prepoznavanje bolesti i kontinuirano praćenje bolesnika, u skladu sa preporukama Evropske mreže za inovativnu dijagnozu i tretman hronične neutropenije (European Network for Innovative Diagnosis and Treatment of Chronic Neutropenias). Slučaj prikazuje četrdesetogodišnju ženu, koja se javila Hematološkoj klinici Univerzitetskog kliničkog centra u Nišu radi redovne kontrole zdravlja i krvne slike. Naime, kod bolesnice su u 21. godini, nakon prvog porođaja, uočene neutropenija i anemija. Laboratorijski parametri, izuzev broja neutrofila, bili su u fiziološkim granicama. Periferni razmaz krvi takođe nije odstupao od fiziološkog izgleda. Rezultati imunoloških analiza bili su u okviru referentnih vrednosti. Zatim, sprovedeni su testovi, koji su pokazali da ne postoji virusna infekcija koja bi mogla da bude uzrok smanjenog broja neutrofila. Punkcija koštane srži pokazala je uredan nalaz. Hronična neutropenija može biti udružena sa nizom ozbiljnih zdravstvenih komplikacija. Stoga, sugerišemo uvođenje definisanog pristupa identifikaciji, registrovanju, praćenju bolesnika sa hroničnom neutropenijom kroz centralni registar, slično drugim evropskim zemljama.

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**Ključne reči:** hronična idiopatska neutropenija, dijagnostički postupak, registar