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Chronic neutropenia in adults

CLINICAL REVIEW

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Neutrophils are an important component of the innate immune system, and they prevent bacterial and fungal infections by phagocytosis and killing of pathogens. Neutropenia is defined as an abnormally low number of circulating neutrophils, and the term chronic neutropenia is used when it lasts more than three months. The objective of this clinical review is to raise awareness among doctors in Norway of chronic neutropenia and possible causes. A patient with severe neutropenia and fever requires immediate admission to hospital and initiation of empiric sepsis treatment before the cause of neutropenia has been determined, but patients with chronic neutropenia do not always require rapid and extensive workup.

Neutrophils normally make up 45–75 % of the leukocytes in blood. Circulating neutrophils (3–5 % of the body's neutrophils) are in rapid and dynamic equilibrium with an equal quantity of neutrophils adherent to the vascular wall, predominantly in the lungs, liver, spleen and bone marrow (1). Marginated granulocytes form a reservoir that is mobilised when needed, e.g. in case of infection, adrenaline release and physical exertion. The bone marrow has the largest storage pool (approx. 90 %) of mature and more immature granulocytes.

Neutropenia in Caucasian adults is usually defined as neutrophils < 1.5×10^9/L (2) and is classified as mild ($1.0–1.5 \times 10^9$/L), moderate ($0.5–1.0 \times 10^9$/L) or severe (< 0.5×10^9/L) (3). When neutrophils are < 0.2×10^9/L, it is usually referred to as very severe neutropenia. Neutropenia lasting longer than three months is termed chronic neutropenia.

Neutropenia is the result of one of three underlying mechanisms: reduced production, increased immune-mediated destruction or shift of circulating neutrophils to the vascular endothelium or tissues, which is termed margination (4).

Circulating neutrophils represent a small proportion of the available pool of granulocytes. A low blood neutrophil count does not necessarily entail an increased risk of infection, particularly not if the skin and mucosal barriers are intact. The incidence of neutropenia varies with age, sex, ethnic origin and concurrent immune disease (3, 5). Neutropenia in a patient usually requires investigation of the underlying cause and, if necessary, referral to hospital.

Chronic neutropenia has been discussed in the Journal of the Norwegian Medical Association previously (6). The objective of another discussion is that we quite often see neutropenia as an incidental finding. Routine blood cell counts revealed neutropenia in 1 % of individuals in a Danish article from 2016 (7). In Norway, we have gained a considerable immigrant population who have chronic neutropenia based on the Norwegian reference range, but who are not unwell and do not require extensive workup. We would like to give doctors in Norway up-to-date information about the investigation and possible treatment of patients with chronic neutropenia of unknown cause. The evidence is based on a non-systematic search in PubMed and the authors' own experiences from clinical practice.

Causes of chronic neutropenia

The most common causes of chronic neutropenia in adults are benign ethnic neutropenia and dose-related drug-induced neutropenia. Diseases that are associated with reduced production of neutrophils are often associated with a susceptibility to infection. The inherited bone marrow failure syndromes can emerge in adulthood, but are usually identified in childhood following repeated infections (6). Below we discuss four of the more common forms of neutropenia in adults, which illustrate differences in the need for investigation and treatment.

Benign ethnic neutropenia

The term benign ethnic neutropenia is used when healthy individuals have neutrophils < 1.5×10^9/L. Individuals with the condition do not have any increased susceptibility to infection because neutrophils can be mobilised from a normal reservoir as required. Benign familial neutropenia is phenotypically similar to benign ethnic neutropenia, but, although clearly hereditary, it is not linked to a particular ethnic group (2).

Benign ethnic neutropenia is the most common form of neutropenia worldwide. The condition occurs in 25–50 % of people of African descent, in some ethnic groups from the Middle East (including Yemen, Jordan, Israel) and in descendants of these population groups in other parts of the world (2, 8). It is characterised by mild or moderate lifelong neutropenia, while other blood cells are normal, with normal granulocyte morphology (8).

It has been demonstrated that homozygosity for a single-nucleotide polymorphism (rs2814778 SNP) in the Duffy antigen receptor for chemokines (DARC) gene (also called atypical chemokine receptor 1, ACKR1) is responsible for benign ethnic neutropenia (9). The gene codes for the Duffy blood group antigen (Fy^a and Fy^b), a chemokine receptor on the surface of red blood cells which the parasite *Plasmodium vivax* uses to invade red blood cells. Therefore, carriers of two null alleles of the DARC gene are protected against *P. Vivax* infection (10). Absence of ACKR1 expression gives rise to phenotypically

distinct neutrophils that readily leave the circulation, causing neutropenia (11). In Norway, we see benign ethnic neutropenia particularly in immigrant groups from the Horn of Africa.

Congenital neutropenia

Patients with congenital neutropenia usually have neutrophils < 0.5×10^9/L, not necessarily the whole time, but occasionally. The incidence in Sweden is estimated to be 10/million/year (12). These patients have a lifelong history of susceptibility to infection, frequent treatment with antibiotics and hospital admissions. Aphthous ulcers (stomatitis), gum inflammation (gingivitis) and loosening of teeth are very common manifestations.

In cyclic neutropenia, the symptoms fluctuate, with aphthae and severe inflammatory symptoms approximately every three weeks. Neutrophil count is < 0.2×10^9/L when patients have symptoms, but normal or only mildly decreased in the symptom-free phase of the cycle. The cyclical variation will usually be detected by measuring neutrophils three days a week for a six-week period.

Congenital neutropenia often involves a monogenic disease (Table 1), but not always. If no germline mutations can be detected as a cause of congenital neutropenia, the term chronic idiopathic neutropenia is used.

Table 1

Monogenic disease variants in neutropenia detected in adult patients in Norway

Gene	Chromosome	Protein	Inheritance	Clinical finding
ELANE	19	Neutrophil elastase	Autosomal dominant	Cyclic neutropenia
G6PC3[1]	17	Glucose-6-phosphatase catalytic subunit 3	Autosomal recessive	Chronic neutropenia
CSF3R[2]	1	Colony-stimulating factor 3 receptor	Autosomal dominant	Chronic neutropenia
WAS [3]	X	Wiskott-Aldrich syndrome protein	X-linked	Chronic neutropenia
CXCR4	2	CXC receptor 4	Autosomal dominant	WHIM syndrome[4]
CD40LG		CD40 ligand	X-linked	Chronic neutropenia and hypogammaglobulinaemia
SDBS[5]	7	SDBS protein	Autosomal recessive	Chronic neutropenia

[1]Glucose-6-phosphatase catalytic unit

[2]Colony-stimulating factor 3 receptor

[3]Wiskott-Aldrich syndrome

[4]WHIM = warts, hypogammaglobulinaemia, infections, and myelokathexis

[5]Shwachman-Diamond-Blackfan syndrome

Chronic idiopathic neutropenia and autoimmune neutropenia

Chronic neutropenia that cannot be linked to use of medicinal products or a specific genetic, infectious, inflammatory, autoimmune or malignant cause is referred to as chronic idiopathic neutropenia. Chronic idiopathic neutropenia and autoimmune neutropenia are very similar conditions, and it is difficult to differentiate between them because available tests to detect antineutrophil autoantibodies have such low sensitivity and specificity that they should not be used in clinical practice.

The symptoms are as described for congenital neutropenia, but patients do not usually have a lifelong medical history, and the episodes of infection will not usually have been very severe or resulted in hospitalisation.

In children, chronic idiopathic neutropenia may be transient in nature, but this is not usually the case in adults. There are differences in the incidence between the sexes in adults, with the female/male ratio being 8:1 (13).

Neutropenia associated with clonal T-lymphocytes

Acquired neutropenia with clonal T-lymphocytes is a condition found in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, but it is also seen in individuals without any autoimmune disease. The incidence is estimated to be 0.72/million/year in Europe (14). The typical patient is a middle-aged or older person with a mild susceptibility to infection in the form of wound infections, gingivitis and aphthous ulcers, but this condition can also be an incidental finding related to routine examinations.

The condition is suspected if an increased proportion of large granular lymphocytes is found in a blood smear. The diagnosis is confirmed by examination of lymphocytes in the blood with a finding of inverted CD4/CD8 ratio due to an expanded population of $CD3^+/CD8^+/CD57^+$ T-lymphocytes with clonal T-cell receptor rearrangement. In some cases, the clonal T-lymphocytes represent > 0.5×10^9/L, and the diagnostic criteria for large cell granular lymphocyte leukaemia are fulfilled. However, frequently there are fewer clonal T-lymphocytes, so that clinically significant clonal T-cell lymphocytosis is a more accurate term. The expansion of $CD3^+/CD8^+$ T-lymphocytes also does not need to be clonal for neutropenia to occur. Holm et al. demonstrated that polyclonal $CD3^+/CD8^+$ T-lymphocytosis resulted in neutropenia in patients with common variable immunodeficiency (15).

Investigation

Neutropenia can be an incidental finding or a finding related to the investigation of a patient with a susceptibility to infection. Severe isolated neutropenia in adults of Norwegian ethnicity is almost always drug-induced (Box 1) or toxin-induced. In order to evaluate underlying disease, risk and prognosis, it is important to take a detailed case history, including family history, use of medication, current health status and susceptibility to infection (5). Review of previous test results, if these results are available, can clarify whether the neutropenia is recent, has been present for a long time or could be related to infection or initiation of medicinal treatment.

Box 1 Summary of medicinal products frequently associated with neutropenia.

Antibiotic agents

Benzylpenicillin
Amoxicillin
Ceftriaxone
Meropenem
Piperacillin/tazobactam
Vancomycin
Linezolid
Clindamycin
Ciprofloxacin
Trimethoprim/sulfamethoxazole
Metronidazole
Teicoplanin

Non-steroidal anti-inflammatory drugs (NSAIDs)

Ibuprofen
Naproxen

Antiepileptics
Carbamazepine
Levetiracetam

Antipsychotics/antidepressants

Clozapine
Venlafaxine
Amitriptyline

Miscellaneous drugs

Carbimazole
Sulfasalazine
Valganciclovir

Mycophenolic acid
Tacrolimus
Ticlopidine

In healthy individuals from parts of the world where benign ethnic neutropenia is widespread, the condition is verified by Duffy typing. In other individuals with chronic neutropenia, investigation by a haematologist is required for diagnostic elucidation. If symptoms of infection are not prominent, urgent investigation is not required. The haematologist will decide whether investigation is required, and the workup will usually entail bone marrow aspiration/biopsy for morphological, immunological and genetic testing.

Treatment

Benign ethnic neutropenia is not a disease, but rather a normal condition. Therefore, there is no indication for treatment and no need for follow-up or monitoring.

Granulocyte-colony stimulating factor (G-CSF, filgrastim) is the main treatment for congenital chronic idiopathic neutropenia and autoimmune neutropenia where treatment is indicated. Frequent infections involving extensive absence from work or school and/or frequent treatment with antibiotics are a reason for treatment. Filgrastim is administered by subcutaneous injection daily or 2–3 times a week for an indefinite period of time. Treatment is effective in almost all patients, and it is extremely rare for adverse reactions to be so prominent that patients wish to discontinue treatment. In congenital neutropenia with monogenic mutation, there is a risk of developing acute myeloid leukaemia, and it may be appropriate to consider stem cell transplantation in cases of disease progression.

Treatment with filgrastim does not need be stopped in pregnancy. (16). Patients being treated with filgrastim should be monitored in the specialist health service.

In neutropenia caused by clonal T-lymphocytes, the preferred approach is immunosuppressant treatment (cyclosporin, methotrexate or cyclophosphamide) if treatment is required (17).

Conclusion

Not all patients with neutropenia require referral to a haematologist or bone marrow examination. If chronic neutropenia is suspected as an adverse reaction to drug treatment, stopping the treatment is usually sufficient (in consultation with a haematologist). Benign ethnic neutropenia is not a disease and does not require follow-up. Other forms of neutropenia will usually require

investigation in the specialist health service for diagnostic elucidation, but treatment is not always needed. The extent of susceptibility to infection will determine the indication for treatment.

The article has been peer-reviewed.

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