Chronic neutropenia in children – diagnostics, therapeutic management and prophylaxis

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Abstract

Chronic neutropenia (CN) is a rare disorder in children. It is defined by an absolute neutrophil count (ANC) below 1500 cells per cubic microliter of peripheral blood, lasting for at least 6 months. It can be acquired or congenital. More frequent – acquired chronic neutropenia is mainly caused by: malnutrition, exposure to drugs, chemical compounds and viral infections. CN is the cardinal symptom of some rare, hereditary entities such as: chronic benign familial neutropenia, Shwachman-Diamond syndrome (SDS), Kostmann syndrome (KS), cyclic neutropenia (CyN), glycogen storage disease type 1b (GSD1b). It may be also associated with primary immunodeficiency (PID), organic acidaemia or autoimmune disease. Diagnostics requires: detailed medical history of a child, repeated complete blood counts (CBS) including absolute neutrophil count (ANC), bone marrow aspirate, granulocytic antibodies – in cases of severe neutropenia, sometimes – immunologic investigation. Therapeutic management depends on the clinical entity, patient's age and severity of clinical course; it includes antibiotic and vaccine prophylaxis, in selected children – chronic rHuG-CSF-treatment or haematopoietic stem cell transplantation (HSCT) from an HLA – identical related or unrelated donor, especially in children suffering from the diseases connected with relatively high risk of malignant myeloid transformation such as: KS, SDS and Fanconi anaemia (FA). Currently, autoimune neutropenia of infancy (AIN), a benign and self-limiting condition, is more often diagnosed by anti-neutrophil antibodies detection, in children under 5 years of age.

Key words: *chronic neutropenia, primary immunodeficiency, anti-granulocytic antibodies, rHuG-CSF, haematopoietic stem cell transplantation.*

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Introduction

Chronic neutropenia is a heterogenous group of both, inherited and acquired disorders, affecting children and adults. It is defined by an absolute neutrophil count (ANC) decreased below 1500 cells per cubic microliter of peripheral blood, lasting for at least 6 months [1-3]. It has been classified according to absolute neutrophil count (ANC) as:

- mild neutropenia ANC – 1500-1000/μl;
- moderate neutropenia ANC – 1000-500/μl;
- severe neutropenia ANC – <500/μl;
- agranulocytosis ANC – <100/μl.

Due to physiological lymphocytosis, the diagnosis of neutropenia in infancy is established when ANC decreases below 1000/μl.

The reduced number of circulating neutrophils makes patients vulnerable to infection. The risk of serious infection increases when ANC becomes lower than 500/μl and it raises rapidly when ANC is below 200/μl.

Chronic periodontitis, painful aphtae, recurrent otitis media, sinusitis, tonsillitis, subcutaneus and various organ abscesses, suppurative lymphadenitis, poor wound healing and, in the most seriously ill, recurrent, severe bacterial infections such as: sepsis, meningitis, osteomyelitis and pneumonia compose a typical clinical picture of chronic neutropenia. The most common organisms, infecting granulocytopenic children, are: staphylococci, streptococci, gram-negative bacteria (especially *E. coli*, *Pseudomonas sp.* and *Heamophilus influenzae*) and anaerobes. Noteworthy – fungal infections are not the part of 'pure' (without any

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Table 1. Causes of chronic neutropenia in children

Inherited neutropenia	**Acquired neutropenia**
– Kostmann syndrome (KS)	**bone marrow dysfunction caused by:**
– Shwachman-Diamond syndrome (SDS)	– drugs – chemical compounds – viruses (EBV, HCMV, HIV, HHV6, PVB19, HAV, HBV, HCV) – irradiation
– chronic benign familial neutropenia (CBN)	
– cyclic neutropenia (CyN)	
– glycogen storage disease type 1 b (GSD1b)	**immunoneutropenia:**
– WASP activation mutation	– alloimmune: • neonatal alloimmune neutropenia (NAIN)
– organic acidaemias: • methylomalonic acidaemia (MMA) • isovaleric acidaemia (IVA) • propionic acidaemia (PA)	– autoimmune: • autoimmune neutropenia of infancy (AIN) • in rheumatic disorders (SLE, ICA) • drug – induced
– Barth syndrome	**bone marrow dysfunction caused by:**
– Fanconi anemia (FA)	– leucaemia, histiocytosis X, MDS – metastases, lymphomas – cystinosis, osteomyelosclerosis – chronic idiopathic neutropenia (CIN) – hypersplenism – malnutrition – vitamine B_{12} deficiency – folic acid deficiency – copper deficiency
– CD40 ligand deficiency/HIGM type I	
– hyper IgM syndrome type III/HIGM t III	
– cartilage-hair hypoplasia (CHH)	
– Cohen syndrome	
– Chediak-Higashi syndrome (CHS)	
– Griscelli syndrome type II (GSII)	
– Bruton agammaglobulinaemia (XLA)	
– myelokathexis and WHIM syndrome	
– WHIM (warts, hypogammaglobulinaemia, infections, myelokathexis)	

co-existing immune or haematologic defect) neutropenia, albeit fungi may be involved as secondary infective agents.

Differential diagnosis

The diagnostic management is often difficult as chronic neutropenia may be caused by nearly 30 miscellaneous congenital and acquired entities or conditions [1-4]. They are all listed in table 1.

Chronic neutropenia may be an essential symptom of some extremely rare, inherited diseases such as: congenital agranulocytosis – referred to as Kostmann syndrome (KS), cyclic neutropenia (CyN), glycogen storage disease type 1b (GSD1b), Shwachman-Diamond syndrome (SDS) or be an element, not obligatorily present, of such syndromes as CD40L – deficiency, also referred to as hyper IgM syndrome type I, Fanconi anaemia (FA), cartilage-hair hypoplasia(CHH) [4-9].

Currently, chronic benign familial neutropenia seems to be the most common inherited form of chronic neutropenia, while Kostmann syndrome remains the most severe one, if untreated.

It is worth noting that chronic neutropenia may be also associated with metabolic inborn disorders (GSD1b, methylomalonic acidaemia – MMA, isovaleric acidaemia – IVA, propionic acidaemia – PA and 3-methylglutaconic aciduria/Barth syndrome) [10, 11] or primary immunodeficiency (hyperIgM syndrome – HIGM type I and III, X-linked agammaglobulinaemia – XLA, Chediak-Higashi syndrome – CHS, Griscelli syndrome type II – GS II, common variable immunodeficiency – CVID, myelokathexis and WHIM syndrome, autoimmune lymphoproliferative syndrome – ALPS, Wiskott-Aldich syndrome – WAS, selective IgA deficiency – IGAD and reticular dysgenesis) [1, 3, 12-15]. That is why immunologic and metabolic investigation is of great importance in children affected with chronic neutropenia.

Acquired chronic neutropenia, which is more frequent than congenital forms, may be caused by drugs (listed in table 2), chemical compounds (present in: paints, organic solvents, pesticides etc), viruses (*Epstein-Barr virus* – EBV, *Human cytomegalovirus* – HCMV, *Human immunodeficiency virus* – HIV, *Human herpes virus type 6* – HHV6, *Parvovirus B19* – PVB19, *Hepatitis A virus* – HAV, *Hepatitis B virus*

Table 2. Drugs associated with neutropenia

analgetics	acetaminophen, aminopyrine, metamizole
antibiotics	cephalosporins, clindamycin, chloramphenicol, doxycycline, gentamycin, griseofulvin, isoniazid, metronidazole, penicillins, rifampin, streptomycin, vancomycin, imipenem
anticonvulsants	carbamazepine, phenytoin, primidone, valproic acid
anti-histaminic drugs	cimetidine, ranitidine
anti-inflammatory drugs	aminophenazon, fenoprofen, ibuprofen, indomethacin, gold salts
antithyroid agents	carbimazole, methylthiouracil, prophylthiouracil
antimalarians	amodiaquine, dapsone, hydroxychloroquine, pyrimethamine, quinine
cardiovascular drugs	captopril, hydralazine, methyldopa, pindolol, propranolol, quinidine
diuretics	acetazolamide, bumetanide, chlorothiazide, hydrochlorothiazide, chlorthalidone, methazolamide, spironolactone
hypoglycaemic agents	chlorpropamide, tolbutamide
neuropharmacologic agents	phenothiazines (chlorpromazine, clozapine, prochlorperazine, promazine), meprobamate
miscellaneous drugs	allopurinol, colchicine, d-penicillamine, gancyclovir, levamisole, levodopa, nitrofurantoin, metoclopramide, sulfonamides

– HBV, *Hepatitis C virus* – HCV), bacteria (*Mycobacterium tuberculosis*), parasites (*Toxoplasma gondii*), severe malnutrition (the main causative factor worldwide) and conditions leading to bone marrow dysfunction [1-3, 7, 16].

An important group, leading to chronic granulocytopenia, includes immune diseases, among them autoimmune neutropenia of infancy (AIN) and neonatal alloimmune neutropenia (NAIN) being the most common entities [17-19]. The diagnostics of AIN and NAIN requires detection of neutrophil antibodies in patients' sera [19,20]. Autoimmune neutropenia may be the part of: Evans syndrome [21], rheumatic disorder such as systemic lupus erythematosus (SLE) and idiopathic chronic arthritis (ICA) or primary immunodeficiency, like common variable immunodeficiency (CVID), autoimmune lymphoproliferative syndrome (ALPS) or isolated IgA deficiency (IGAD); it may also be induced by drugs, which are able to act as haptens and cause antibody formation (e.g. penicillin, gold salts, diuretics) [1].

Diagnostic management

There is no common approach to diagnostics of a child with chronic neutropenia – it depends on patient's age at the presentation, the depth of neutropenia, oscillations of ANC, the severity and aethiology of infections. The most important diagnostic tools are bone marrow smears and granulocytic antibodies evaluation. The differential diagnostics of chronic neutropenia, based on a bone marrow aspirate and anti--neutrophil antibodies screening, is shown in figure 1.

Screening for granulocytic antibodies is recommended mainly in children presenting with severe neutropenia (ANC <500/μl) and should consist of 3 tests: MAIGA (monoclonal antibody specific immobilization of granulocyte antigens), GIFT (granulocyte immunofluorescence test) and GAT (granulocyte agglutination test). The detection of these antibodies is difficult, therefore to prevent diagnostic mistakes, in cases strongly suspected of AIN, it is recommended to repeat all 3, mentioned above, tests after 4-6 weeks. Notabene: in neonates and infants suspected of NAIN we perform anti--neutrophil antibodies screening in their mothers' sera.

In some cases, due to a relatively high incidence of chronic neutropenia in course of primary immunodeficiencies, immunologic investigation should be performed. The basic immunologic evaluation includes: quantitive immunoglobulins (IgA, IgG, IgM, IgE), C3 and C4 components of complement, post-vaccination antibody titers, lymphocytes subsets, expression of CD40L on CD4+ lymphocytes – in boys with hypogammaglobulinaemia and Wiskott-Aldrich protein expression in boys with thrombocytopenia.

Additional, non-haematological symptoms may also be helpful. Chronic diarrhea, failure to thrive, microcephaly or sceletal abnormalities, albinism, warts, congenital cardiac defect or cardiomyopathy and co-existing laboratory aberrations such as: elevated aminotransferases, hypoglycaemia, lactic acidosis, elevated faecal fat, abnormal GC/MS in urine belong to typical clinical picture of various entities associated with chronic neutropenia. In this paper we present a diagnostic algorithm (figure 2), based on such, additional to chronic neutropenia, symptoms that may help to establish the diagnosis. This algorithm, inspired by diagnostic flowchart of Severe Chronic Neutropenia International Registry (SCNIR), has been subsequently developed basing on own experience of the Department of Immunology of Children's Memorial Health Institute in Warsaw.

Presentation of chronic neutropenia in the first weeks of life may suggest either inherited disease (like Kostmann syndrome, GSD1b, organic acidaemia) or neonatal allo-

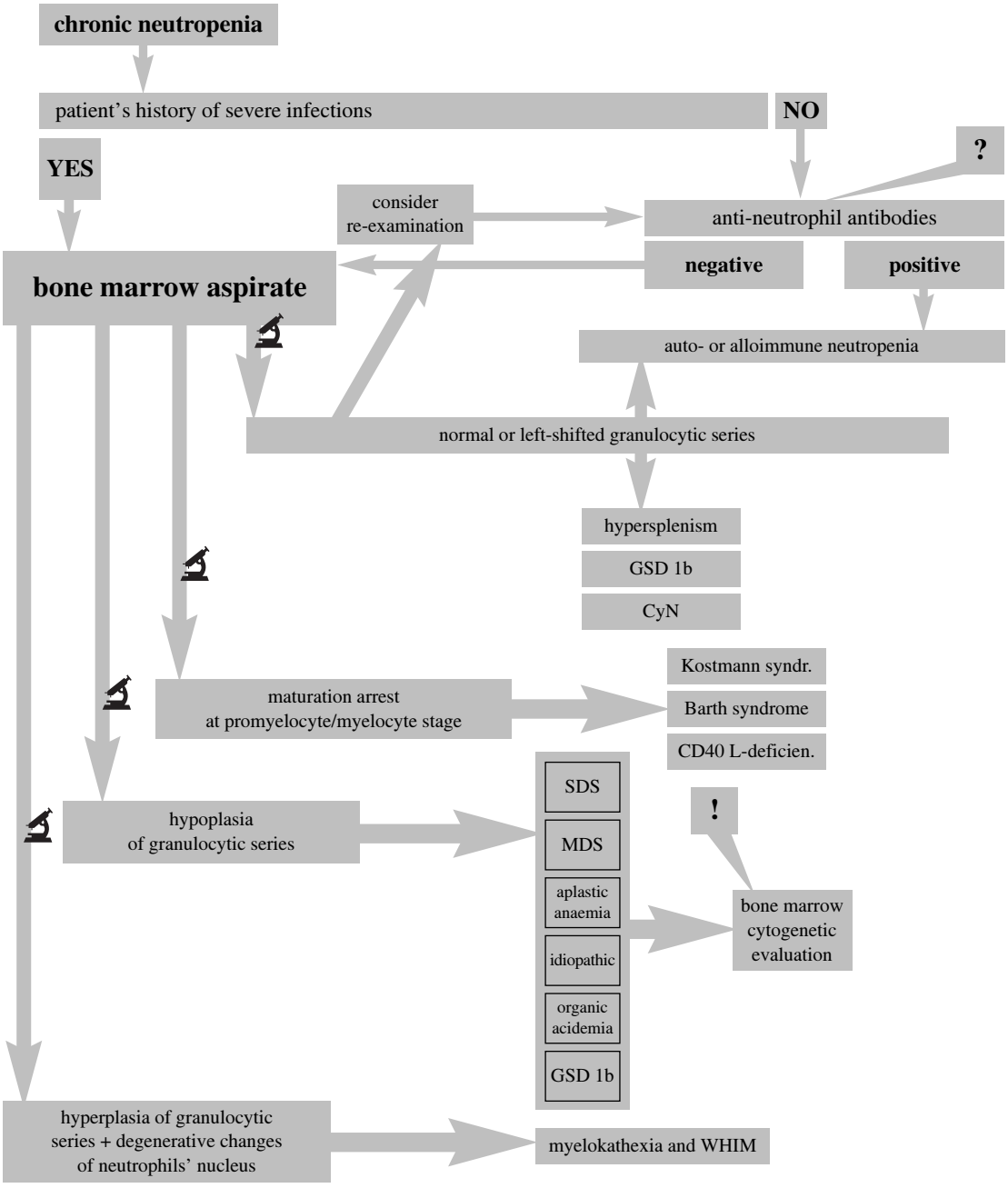

Fig. 1. Differential diagnostics of CN in children

immune neutropenia (NAIN), which may occur during first pregnancy [20]; albeit infections, potentially inducing neutropenia, caused by such pathogens as: HCMV, PVB19, HHV6 or *Toxoplasma gondii* should also be excluded.

In a child older than 6 months, without a medical history of life-threatening infections with weight and length/height adequate to age, the most possible diagnosis is autoimmune neutropenia of infancy (AIN) [17-19]. In such cases a bone marrow aspirate is necessary only for patients whose plasma was tested for anti-neutrophil antibodies and all 3, above mentioned diagnostic tests, were negative.

If life-threatening bacterial infections have occurred or a child presents with growth retardation, it is recommended to start the diagnostic management with bone marrow

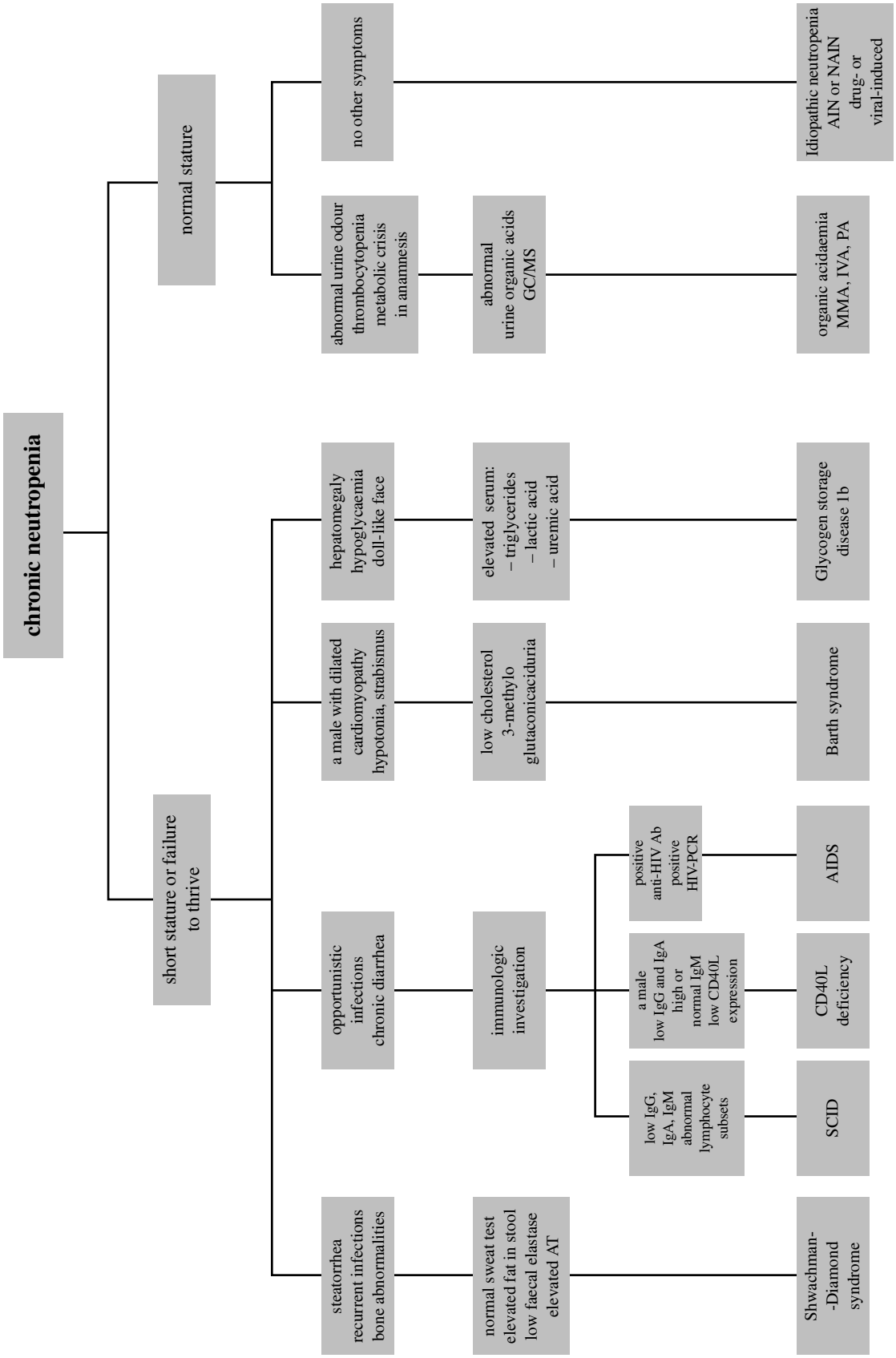

Fig. 2. Diagnostic algorithm for children with chronic neutropenia

aspirate. No evidence of maturation arrest, indicating first of all Kostmann syndrome, but also observed in boys affected with Barth syndrome and CD40L – deficiency, requires further differential diagnostics to rule out Shwachman-Diamond syndrome, severe combined immunodeficiency – SCID, GSD1b and HIV-infection. The diagnostic evaluation should include tests listed in figure 2.

In children older than 6 years, like in adults, the most frequent cause leading to chronic neutropenia is exposure to drugs or chemical compounds. Table 2 presents commonly used drugs that have been reported to induce neutropenia in different mechanisms. Some drugs induce neutropenia by direct inhibition of myelopoiesis, for instance – carbamazepine, valproic acid, β-lactams. Others cause idiosyncratic reactions, that affect only susceptible individuals – chloramphenicol or sulphonamides are the best examples. Some drugs lead to bone marrow aplasia in every treated individual, if administered in large enough doses (phenytoin, phenobarbital), others act as haptens and induce anti-neutrophil antibody formation (penicillin, gold salts, aminopyrine, antithyroid drugs) [1].

Table 2 includes such popular agents as antibiotics, antipyretics or anti-convulsants. That accounts for significance of information about any new drugs or recent changes of treatment obtained from the child's parents. The inquiry should be extended to the period of approximately 3 months, as the offending drug may no longer be in use.

In patients of this age group the evaluation of possible active or recent, viral infection should also be performed. Such viruses as *Epstein-Barr virus* (EBV), *Human cytomegalovirus* (CMV), HHV6, hepatitis A, B or C virus and HIV are well-known for their myelosupressive properties [1, 3, 7, 16].

A history of periodically recurring infections is highly suggestive of cyclic neutropenia. In those children, 3 complete blood counts (CBC) weekly for at least 6 weeks should be performed to document a cycle of an absolute neutrophil count oscillation.

A history of autoimmune disease, particularly systemic lupus erythematosus or idiopathic chronic arthritis, may indicate autoimmune mechanism of neutropenia and anti--neutrophil antibodies evaluation should be ordered. In some, difficult to diagnose, cases chronic neutropenia and the detection of granulocytic antibodies may be the sole or primary manifestation of autoimmune disease, therefore antinuclear antibodies (ANA), anti-double stranded DNA antibodies (dsDNA), rheumatoid factor (RF), C3 and C4 components of complement, total haemolytic complement assay-CH50 and circulating immune complexes (CIC) should be tested in children, especially girls, with chronic neutropenia of unknown origin.

The co-incidence of opportunistic infections may indicate both, primary immunodeficiency or HIV-infection. A family history of an infant or a little child's death may suggest either primary immunodeficiencies or inborn metabolic disorders, like methylomalonic acidaemia (MMA), isovaleric acidaemia (IVA), propionic acidaemia (PA) or Barth syndrome (in boys).

Chronic idiopathic neutropenia (CIN) remains the diagnosis of exclusion, when bone marrow injury, primary immunodeficiency, metabolic disorder, autoimmune entities and other known causes of chronic neutropenia have been excluded.

Therapeutic management and prophylaxis

Therapeutic methods in children affected with chronic neutropenia depend on entity, patient's age and the severity of clinical course of disease. The treatment includes: recombined human granulocyte colony stimulating factor (rHuG-CSF), antibiotic prophylaxis and haematopoietic stem cell tranplantation (HSCT) [1, 3, 10, 23, 24]. Vaccines against encapsulated bacteria, such as: *Haemophilus influenzae type B*, pneumococci, *Neisseria meningitidis type A* and/or *C* are recommended for all children presenting with chronic neutropenia. On the other hand – live vaccines against measles, mumps, rubella and chicken pox must not be performed in the ill presenting with ANC below 1000/μl.

Before rHuG-CSF-teatment was available, most children with severe congenital forms of chronic neutropenia, died from fatal bacterial infections within first years of life, as no other therapy to correct neutropenia was known. Although antibiotics could prolong patients' life, but to overcome serious, systemic, bacterial infection – both, anti-bacterial drugs and neutrophils, are necessary. Glucocorticosteroids may transciently elevate ANC in patients with AIN or idiopathic neutropenia, but they are unsuitable for long-term treatment because of their side effects [17, 18].

Various intravenous immunoglobulin preparations have also been used, but benefits are transient and the cost of such a treatment is very high [23].

Data collected by SCNIR since 1994 proved the effectiveness and reletive safety of long-term rHuG-CSF-therapy of patients with severe chronic neutropenia [23]. These data have indicated that rHuG-CSF is a treatment of choice in patients affected with Kostmann syndrome, GSD1b and cyclic neutropenia. This drug may be considered in individuals with Barth syndrome, myelokathexia, Shwachman-Diamond syndrome and all cases of severe chronic neutropenia, if accompanied by serious, life-threatening bacterial infections.

The dosage of rHuG-CSF differs from patient to patient and in various entities. It is relatively higher in children with KS or SDS than in CyN, CIN or GSD1b [3, 7, 8, 11, 23, 24].

Data on patients with severe chronic neutropenia, collected by SCNIR since March 1994, indicate that about 92% of individuals with Kostmann syndrome respond well to rHuG-CSF – they achieve an increase of ANC >1000/μl; the curative dose varies between 0.5-120 μg/kg/day. In patients non-responding to rHuG-CSF, even in high doses of 100-120 μg/kg/day within 14 days, the only therapeutic option is HSCT. Therefore the search for an HLA-matched, bone marrow donor should be started immediately [23].

For 13 years SCNIR has collected data on approximately 800 patients affected with various types of severe chronic neutropenia. These data clearly indicate that patients with KS and SDS have an increased risk of developing MDS/AML, compared to healthy individuals [23-25]. No cases of malignant myeloid transformation have been reported in children with cyclic or idiopathic neutropenia. Unfortunately a few cases of progression to leucaemia have been reported in patients with GSD1b [29]. Therefore, bone marrow aspiration, myelogram and cytogenetic evaluation are strongly recommended yearly in the ill put on regular rHuG-CSF-treatment, especially in those affected with KS, SDS and GSD1b [23].

It is worth mentioning, that the data collected by SCNIR revealed that about 60% of severe congenital neutropenia patients transforming into MDS/AML had co-existing partial or complete loss of chromosome 7 (7q – or monosomy 7) in their marrow cells. Some patients, with leucaemic transformation, had activating RAS oncogene mutations, while others developed point mutations in the gene for G-CSF receptor, resulting in a truncated C-terminal cytoplasmic region of G-CSFR, which is crucial for maturation signaling [23]. Kostmann syndrome and Shwachman-Diamond syndrome, if accompanied by such chromosomal aberrations as monosomy 7 or trisomy 21, becomes an indication for HSCT due to high incidence of malignant transformation to MDS/AML.

Adverse events (AE) documented in patients treated with rHuG-CSF include: splenomegaly and/or hepatomegaly, thrombocytopenia, anaemia, pains of bones and/or muscles, osteoporosis/osteopenia, vasculitis, glomerulonephritis or persistent haematuria, headache, fever, nausea, vomiting, loss of apetite. Elevated activity of serum aminotransferases, lactic dehydrogenase, alcalic phosphatase and increased concentration of uremic acid are common laboratory aberrations, connected with rHuG-CSF-treatment. Most AE are transient and mild, albeit cases of splenectomy, due to severe hypersplenism, in children with chronic severe neutropenia cured with rHuG-CSF have been reported by SCNIR [23].

In course of chronic neutropenia, antibiotic anti--bacterial prophylaxis is essential for children under 12 months of age; in older patients it should be considered individually [30]. It is recommended for children with cyclic neutropenia (CyN), GSD1b, SDS – if not treated with rHuG-CSF, as well as for individuals with ANC <500/μl when accompanied by occurrance of severe bacterial infections. Antibiotic is usually used in one daily dose – e.g. amoxicillin 20 mg/kg/day. It has been proved that such a treatment decreases both, the frequency and severity, of infectious complications caused by bacteria [30].

Professional dental care is next, very important part of curing patients with chronic neutropenia.

In the end, it is worth to mention that neutropenic individuals have to avoid the usage of drugs known for their myelospressive properties.

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References

1. Janicki K. Choroby układu białokrwinkowego. In: Hematologia. PZWL. Warszawa, 2001 (in Polish).
2. Matysiak M. Zaburzenia dotyczące układu granulocytarnego. In: Hematologia w praktyce pediatrycznej. Ed. M Matysiak. PZWL, Warszawa. 2002, 56-59 (in Polish).
3. Klaudel-Dreszler M, Irga N, Bernatowska E (2004): Przewlekła neutropenia u dzieci – diagnostyka różnicowa oraz leczenie. Stand Med 12: 1300-1306 (in Polish).
4. Ancliff PJ (2003): Congenital neutropenia. Blood Rev 17: 209-216.
5. Dror Y, Freedman MH (2002): Shwachman-diamond syndrome. Brit J Haematol 118: 701-713.
6. Levy J, Espanol-Boren T, Thomas C et al. (1997): Clinical spectrum of X-linked hyper-IgM syndrome. J Pediatr 131: 47-54.
7. Boxer LA (2003): Zaburzenia układu granulocytarnego. Ped po Dypl 7 (in Polish).
8. Zetterström R (2002): Kostmann disease – infantile genetic agranulocytosis: historical views and new aspects. Acta Pediatr 91: 1279-1281.
9. Kostmann R (1975): Infantile genetic agranulocytosis. A review with presentation of ten new cases. Acta Paediatr Scand 64: 362-368.
10. Leuzzi R, Bánhegyi G, Kardon T et al. (2003): Inhibition of microsomal glucose-6-phosphate transport in human neutrophils results in apoptosis: a potential explanation for neutrophil dysfunction in glycogen storage disease type 1b. Blood 101: 2381-2387.
11. Kelley RI, Cheatham JP, Clark BJ et al. (1991): X-linked dilated cardiomyopathy with neutropenia, growth retardation, and 3-methylglutaconic aciduria. J Pediatr 119: 738-747.
12. Cham B, Bonilla MA, Winkelstein J (2002): Neutropenia associated with primary immunodeficiency syndromes. Sem Hematol 39: 107-112.
13. Dror Y, Sung L (2004): Update on childhood neutropenia: molecular and clinical advances. Hematol Oncol Clin North Am 18: 1439-1458.
14. Irga N, Wierzba J, Brozek J et al. (2003): X-linked agammaglobulinemia (XLA) associated with agranulocytosis – case report. Wiad Lek 56: 7-8 (in Polish).
15. Aprikyan AA, Liles WC, Park JR et al. (2000): Myelokathexis, a congenital disorder of severe neutropenia characterized by accelerated apoptosis and defective expression of bcl-x in neutrophil precursors. Blood 95: 320-327.
16. Berliner N, Horwitz M, Loughran TP Jr. (2004): Congenital and acquired neutropenia Hematology Am Soc Hematol Educ Program: 63-79.
17. Bux J, Behrens G, Jaeger G, Welte K (1998): Diagnosis and clinical course of autoimmune neutropenia in infancy: analysis of 240 cases. Blood 91: 181-186.
18. Lalezari P, Khorshidi M, Petrosova M (1986): Autoimmune neutropenia of infancy. J Pediatr 109: 764-769.
19. Bruin MC, von dem Borne AE, Tamminga RY et al. (1999): Neutrophil antibody specificity in different types of childhood autoimmune neutropenia. Blood 94: 1797-1802.

20. Zupańska B, Uhrynowska M, Guz K et al. (2001): The risk of antibody formation against HNA1a and HNA1b granulocyte antigens during pregnancy and its relation to neonatal neutropenia. Transfus Med 11: 377-382.
21. Mathew P, Chen G, Wang W (1997): Evans syndrome: results of a national survey. J Pediatr Hematol Oncol 19: 433-437.
22. Skopczyńska H, Litwin J, Rump Z et al. (1995): Wpływ leczenia rekombinowanym czynnikiem wzrostu kolonii granulocytarnych na przebieg zakażeń u dzieci z ciężką przewlekłą wrodzoną neutropenią. Klinika 8: 65-67 (in Polish).
23. Dale DC, Cottle TE, Fier CJ et al. (2003): Severe chronic neutropenia: treatment and follow-up of patients in the Severe Chronic Neutropenia International Registry. Am J Hematol 72: 82-93.
24. Calderwood S, Kilpatrick L, Douglas SD et al. (2001): Recombinant human granulocyte colony-stimulating factor therapy for patients with neutropenia and/or neutrophil dysfunction secondary to glycogen storage disease type 1b. Blood 97: 376-382.
25. Freedman MH, Alter BP (2002): Malignant myeloid transformation in congenital forms of neutropenia. Isr Med Assoc J 4: 1011-1014.
26. Bonilla MA, Dale D, Zeidler C et al. (1994): Long-term safety of treatment with recombinant human granulocyte colony--stimulating factor (r-metHuG-CSF) in patients with severe congenital neutropenias. Br J Haematol 88: 723-730.
27. Freedman MH, Alter BP (2002): Risk of myelodysplastic syndrome and acute myeloid leukemia in congenital neutropenias. Semin Hematol 39: 128-133.
28. Smith OP, Hann IM, Chessells JM et al. (1996): Haematological abnormalities in Shwachman-Diamond syndrome. Br J Haematol 94: 279-284.
29. Pinsk M, Burzynski J, Yhap M et al. (2002): Acute myelogenous leukemia and glycogen storage disease 1b. J Pediatr Hematol Oncol 24: 756-758.
30. Klaudel-Dreszler M, Pietrucha B, Skopczynska H et al (2007): Chronic neutropenia – experience from the Department of Immunology, Children's Memorial Health Institute. Med Wieku Rozwoj 11: 145-152 (in Polish).