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REVIEW

Chronic neutropenia: how best to assess severity and approach management?

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ABSTRACT

Introduction: Neutropenia is a relatively common finding in medical practice and the medical approach requires a gradual and pertinent diagnostic procedure as well as adapted management.

Areas Covered: The area of chronic neutropenia remains fragmented between diverse diseases or situations. Here physicians involved in different aspects of chronic neutropenia gather both the data from medical literature till the end of May 2021 and their experience to offer a global approach for the diagnosis of chronic neutropenia as well as their medical care.

Expert opinion: In most cases, the neutropenia is transient, frequently related to a viral infection, and not harmful. However, neutropenia can be chronic (i.e. >3 months) and related to a number of etiologies, some clinically benign, such as so-called 'ethnic' neutropenia. Autoimmune neutropenia is the common form in young children, whereas idiopathic/immune neutropenia is a frequent etiology in young females. Inherited neutropenia (or congenital neutropenia) is exceptional, with approximately 30 new cases per 10^6 births and 30 known subtypes. Such patients have a high risk of invasive bacterial infections, and oral infections. Supportive therapy, which is primarily based on daily administration of an antibiotic prophylaxis and/or treatment with granulocyte-colony stimulating factor (G-CSF), contributes to avoiding recurrent infections.

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Neutropenia; children; gcsf; diagnostic evaluation; classification

1. Introduction

Neutropenia is a relatively frequent finding in both pediatric and adult patients, partially driven by how common blood counts are assessed in routine diagnostics. The vast majority of isolated neutropenias are transient, and most often secondary to a viral or bacterial infection and less commonly presenting with malignant hematological disease. Neutropenia can also be chronic, defined as lasting longer than 3 months, which can be caused by several etiologies such as 'ethnic' neutropenia, autoimmune neutropenia in young children, idiopathic/immune neutropenia in young adults, and genetic neutropenia.

2. Methods

Here, the experience of physicians involved in different aspects of chronic neutropenia was combined with data from the medical literature to offer a global approach for the diagnosis and care of chronic neutropenia. To analyze the medical literature, the Medline database was scanned to the end of May 2021 using the key words 'chronic neutropenia' and 'congenital neutropenia.' The names of all identified genes reported in congenital neutropenia (e.g. ELANE, SBDS, HAX1) were also used to identify the literature. The bibliography of each paper was read to identify additional papers. According to evidence-based methodology, the grade of evidence is extremely low and, to the best of our best knowledge, we may have identified only one randomized study that evaluated the impact of Granulocyte-Colony Stimulating factor (GCSF) in chronic neutropenia [1], and the number of cohort studies that included more than 100 patients and focused on aspects of monogenic neutropenia was <15 [2,3,4,5,6,7,8,9,10,11,12,13,14]. This underlines the real difficulties in collecting data and organizing clinical trials and cohorts in this medical area, and explains why many clinical decisions are still based on expert opinion, rather than large cohort studies.

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Article highlights

- There is much information available in the literature concerning neutropenia related to chemotherapy, but very little regarding chronic neutropenia even though management is very different than chemotherapy induced neutropenia.
- Chronic neutropenia is a very common finding, as blood count is now a very common clinical test
- The first step of the medical management of a chronic neutropenia is a specific diagnosis. The most frequent cause of chronic neutropenia is chronic benign neutropenia, frequently associated with the Duffy Null phenotype most commonly seen in those of African ancestry.
- Other benign causes of neutropenia are post viral neutropenia, auto immune neutropenia in young children, idiopathic/immune neutropenia in young adults.
- Congenital neutropenia or inherited neutropenia –i.e. chronic neutropenia related to monogenic forms of neutropenia – is a very rare cause of chronic neutropenia, usually diagnosed because it is associated with severe infections, recurrent oral infections and associated organ dysfunction.
- Medical care should be adapted to the clinical severity of the neutropenia, some benign situations necessiting no medical intervention, while some other situations necessitate medical intervention, ranging from prophylactic antibiotic therapy, G-CSF therapy or definitive cure by allogeneic hematopoietic stem cell transplantation.

3. Definition

Neutropenia is defined as an absolute neutrophil count (ANC) of less than 1.5 x 10^9/L [15,16]. The neutropenia is chronic if it persists beyond 3 months. In the medical literature, some terms are commonly used to qualify the neutropenia, such as benign or severe, and mild and profound. The definitions of such qualifications are frequently not 'self-explanatory' or explicit. In an attempt to clarify, we consider benign and severe as qualifications of the clinical infections resulting from the neutropenia. Mild and profound are qualifications of the ANC, with profound neutropenia being used if the ANC is < 0.5 x 10^9/L and mild as an ANC above that threshold; moderate is also considered if ANC is > 1 x 10^9/L. Neutropenia is classified as permanent if it is present in all blood counts and intermittent if there are periods of spontaneous correction of the neutropenia. If the periodicity of the episodes of neutropenia is approximately 21 days, the neutropenia is said to be 'cyclic.' This implies a cyclical, stable, and reproducible phenomenon, which is rarely observed in current practice [17].

4. Clinical consequences

4.1. Infections

The first clinical consequence of neutropenia is often infections. These infectious consequences correlate primarily with the total number of neutrophils in the body more than with the blood count. The circulating neutrophils, which define neutropenia in a blood test, represent only 1–5% of the total granulocytes in the body, approximately 35 × 10^7 per kg, compared to 75 × 10^8 granulocytes in the bone marrow pool [18,19]. A decrease in the number of circulating neutrophils does not, in the vast majority of cases, translate into a very large decrease in the total number of neutrophils in the body [15]. However, typically the results of blood tests are extrapolated to the overall situation in the body. This is relevant when there is a parallel between the number of blood neutrophils and the overall number of neutrophils, such as during chemotherapy or after bone marrow transplantation. There are also many situations in which the neutropenia, including very profound neutropenia, has minimal or no infectious consequence because the overall total body neutrophil count is not affected. At contrary, ELANE neutropenia can be consider as a model of 'pure' chronic neutropenia and data from a cohort of such patients display a overview of the typology of infections which may occur in neutropenia patients [14]. The most frequent sites are mucocutaneous; ear, nose, and throat; and pulmonary. Oral manifestations (gingivitis, chronic periodontitis, mouth ulcers) are almost constant in cases of profound neutropenia with defects in myeloid differentiation or in severe neutropenia with associated functional defects. Infections are most commonly bacteria, particularly Gram-negative bacilli and staphylococci. Fungal infections are uncommon in chronic neutropenia, except in the context of chemotherapy. Viral infections are also rare in chronic neutropenia unless the neutropenia is associated with a deficit in cellular or humoral immunity.

4.2. Extra-hematopoietic disorders

Extra-hematopoietic dysfunctions are not a consequence of the neutropenia, but rather of a genetic defect if one exists. Monogenic neutropenia, more commonly known as congenital neutropenia, can involve dysfunction of a large number of organs, which may be prominent during clinical examination [16,20,21]. Known extra-hematopoietic disorders are listed in Table 1 according to the gene involved. Notably, such involvement suggests toward a diagnosis and is an important concern in the care of the patients.

5. Evaluation of neutropenia

In adults, neutropenia is estimated to occur in approximately 1% of the non-African population and 5–8% of those of African origin. This frequency is higher in children (4% of children of non-African origin and 12% of children of African origin) [22]. Conversely, congenital neutropenia is extremely rare, with an estimated prevalence of 10^{-5} [23,24]. Thus, only approximately 1/1000 cases of chronic neutropenia may relate to a genetic origin. Among the large number of diagnosed neutropenias, only a small minority requires specialized medical exploration whereas simple monitoring over a few months is justified for the vast majority. This emphasizes why the diagnostic process must be performed in two stages. First, it is important to be able to distinguish the severe forms of neutropenia, requiring quick and specialized exploration, from the minor forms, which are best managed with initial monitoring. The history and clinical examination can quickly point to a particular etiology, such as malignant hematological disease, infection, or iatrogenic causes. The circumstances of the diagnosis should also be taken into

Table 1. Hematological features and associated organ dysfunctions observed in congenital neutropenia with associated genetic subtypes: a partial list.

System	Hematological or extra-hematopoietic features	Gene potentially associated
Blood/bone marrow	Myeloid maturation arrest	*ELANE HAX1 WAS G6PC3 CSF3R SRP54 CLPB JAGN1*
	No maturation arrest	*SLC37A4 CXCR4 SBDS VPS13B AP3B1 TCIRG1 G6PC3 JAGN1 CXCR2*
	Myelokathexis	*CXCR4*
	Myelofibrosis	*VPS45 SMARCD2 CXCR4*
	Macrocytosis	*GATA2*
	Monocytopenia	*CXCR4 GATA2 STK4 (MST1) WAS*
	Thrombocytopenia	*SBDS GATA2 G6PC3*
Pancreas	Exocrine pancreatic insufficiency	*SBDS EIF2AK3 G6PC3 JAGN1* DNA mitochondrial deletion
Digestive tract	Chronic diarrhea/even inflammatory bowel disease	*SLC37A4 G6PC3 SMARCD2*
Eyes	Congenital cataract	*CLPB DNM2*
	Retinochoroidal dystrophy	*VPS13B*
Heart	Arrhythmias	*G6PC3*
	Dilated cardiomyopathy	*TAZ*
	Cardiomyopathy	*SBDS*
	Various cardiac malformations	*SBDS CXCR4 G6PC3 STK4*
Skin	Skin xerosis eczema	*SBDS*
	Prominent superficial veins	*G6PC3*
	Poikiloderma	*USB1*
	Partial or complete albinism	*AP3B1 LAMTOR LYST RAB27A*
	Fine, sparse, and light-colored hair	*RMRP*
	Lymphedema	*GATA2*
	Skin angiomatosis	*TCIRG1*
Bone	Metaphyseal dysplasia	*SBDS EFL1 RMRP*
	Facial dysmorphia	*VPS13B*
Central nervous system	Mental retardation	*HAX1 SBDS VPS13B CLPB*
	Epilepsy	*VPS45*
Muscle	Weakness	*G6PC3 DNM2 SBDS*
Metabolic pathway	Insulin diabetes	*EIF2AK3*
	Fasting intolerance and glycogenesis	*SLC37A4*
	3-methyl glucagonic acid	*TAZ CLPB*
Inner ear	Inner ear defect	*GFI1 GATA2*
Urogenital tract	Uropathy	*G6PC3 GATA2*
	Cryptorchidism	*VPS13B G6PC3*
	Nephromegalia	*VPS45*
Dysmorphy	Palatal cleft	*SBDS VPS13B*
	Hyperlaxity	
Various infections	HPV	*CXCR4 GATA2 STK4 (MST1)*
	Mycobacterial	*GATA2 CXCR4*

account, particularly the presence or absence of a viral or serious bacterial infection, pathologies in other organs, or other associated blood abnormalities (anemia or thrombocytopenia) [25]. If there is concern after this evaluation, the patient should be referred to a specialized hematology service. Conversely, if there is no urgent clinical concern (regardless of the neutrophil count), it is not necessary to do a specialized assessment, but rather outpatient follow-up for an observation period of a few months can collect key clinical elements. The vast majority of neutropenias are transient, most often secondary to a viral infection. In the event of chronic neutropenia, several situations can emerge. The entity often referred to as 'benign ethnic neutropenia' is typically a moderate, fluctuating neutropenia (between 0.5 and > 1.5 x 10^9/L) without any clinical consequences in a patient of African or Middle Eastern descent. Autoimmune neutropenia in children, as well as idiopathic neutropenia in adults, is typically a profound chronic neutropenia (< 0.5 x 10^9/L) without clinical manifestations, whereas congenital/inherited neutropenia is most often responsible for severe infections and frequently associated with organ pathologies [25]. A score developed in children can be used to guide the clinician toward genetic or severe neutropenia (Table 2). For first-line biological tests, when faced with chronic neutropenia or neutropenia immediately associated with a severe bacterial infection, it is advisable to, in addition to a complete blood count (CBC), measure immunoglobulins (IgG, IgA, and IgM), determine the lymphocyte immunophenotype, and search for anti-neutrophil antibodies. In current practice, serum antibodies are tested indirectly by granulo-agglutination and granulo-immunofluorescence, followed by Monoclonal antibody immobilization of granulocyte antigens assay (MAIGA), and much more rarely because of difficult realization, directly by looking for fixed antibodies [26,27]. The results of these tests must always be weighed against the clinical tolerance of the neutropenia and the overall situation, regardless of the age of the patient. To establish of the diagnosis of the cyclic neutropenia may be require monitoring of the ANC twice, or at least once, a week for 6–8 weeks. A bone marrow examination at this stage should be reserved for suspected cases of congenital neutropenia, malignancies, or constitutional bone marrow failure. In teenagers and young adults, viral infections (HIV, HCV, HBV), autoimmunity, myeloid and lymphoid malignancies should be ruled out, and cytogenetic bone marrow examinations are mandatory. Genetic research should be indicated by a team experienced in hematology and discussed in a multidisciplinary consultation meeting. Figure 1 provides a diagnostic approach to neutropenia by summarizing the two steps mentioned above.

6. Etiology of neutropenia

Here, we describe the most frequent etiologies of chronic neutropenia (Table 3) from frequent to rare.

Table 2. Diagnostic score for congenital neutropenia in children [25].

Characteristic	Categories	Score
Age at diagnosis	Between 3 months and 1 year	−2
Family history/consanguinity	Yes	6
Any associated morbidity	Yes	6
Severe infections*	Yes	3
Stomatitis or gingivitis	Yes	3
Monocytes > 1.5 × 10^9/L	Yes	3
Hemoglobin <90 g/L or platelets <150 × 10^9/L	Yes	3
SCORE	In a given patient the score is the sum of the different components	

* Cellulitis, pneumonitis, any sepsis, any deep bacterial infections

Scores of −2 to 0 are associated with no risk of congenital neutropenia (0/32); scores of 1 to 5 are associated with a 21% (7/33) risk of congenital neutropenia; scores of 6 to 9 are associated with a 62% risk of congenital neutropenia; and scores ≥ 10 are associated with a high risk of congenital neutropenia (21/21).

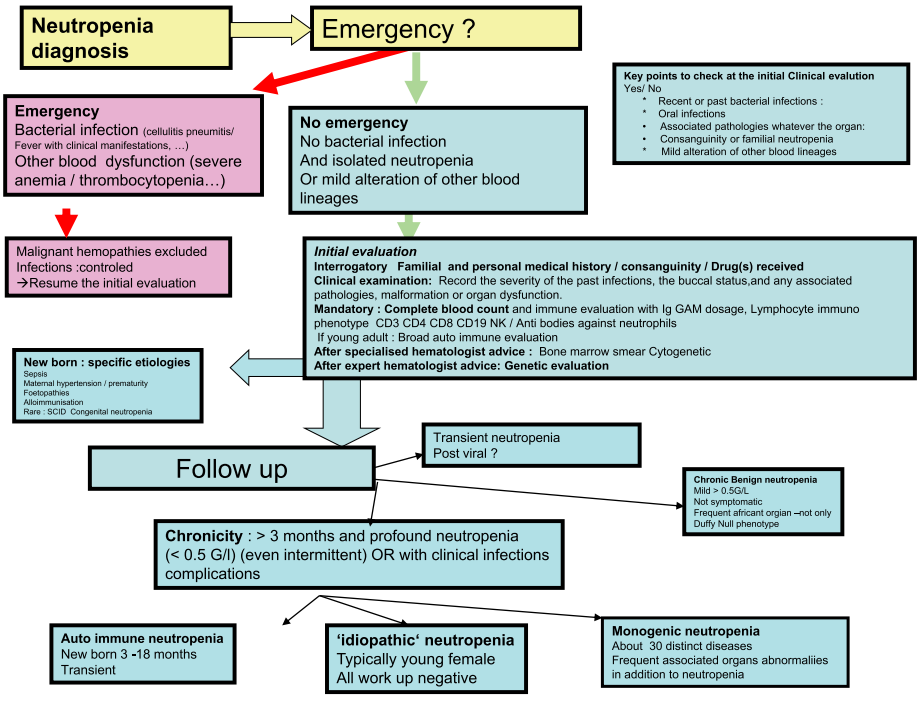

Figure 1. Evaluation of neutropenia: an overview.

6.1. Transient neutropenia

Transient – and acute – neutropenia mainly occur secondary to infections, especially viral infections, and certain drugs. Theoretically, any virus can be responsible, but HIV, cytomegalovirus, EBV, HPV6, and parainfluenza virus, even parvovirus B19, have been described most frequently. It has also been recently associated with bone marrow myeloid maturation arrest and myeloid vacuolization suggestive of congenital neutropenia in SARS-CoV-2 infections [28]. Transient neutropenia is still encountered in bacterial infections, especially in cases of sepsis, salmonella, brucellosis, and parasitic infection (Plasmodium sp.). Transient drug-induced (iatrogenic) neutropenia varies from moderate neutropenia (>0.5 x 10^9/L) well tolerated to severe drug-induced agranulocytosis (<0.1 x 10^9/L). The condition is more common in adulthood and can occur at any time during treatment. The drugs most often incriminated are antiepileptics (e.g. valproate, carbamazepine), antipsychotics (e.g. clozapine), anti-thyroid drugs, antibiotics, and anti-inflammatory drugs [29]. Biotherapy drugs, such as rituximab or anti-TNF drugs, may induce a chronic neutropenia. Lastly, some mineral or vitamin deficiency, such as copper, vitamin B12, or vitamin B9, may be responsible for chronic neutropenia. Copper deficiency is usually observed in a very specific context, such as parenteral nutrition, mental anorexia or nephritic syndrome [22,30–32].

6.2. Chronic benign neutropenia (benign ethnic neutropenia)

Some patients are incidentally found to have chronically lower peripheral neutrophil counts unaccompanied by infectious manifestations or stomatologic involvement. This is especially common in people of African or Arabic ancestry. Individuals with a persistent absolute neutrophil count (ANC) <1.5 x 10^9/L without clinical consequence are often described as having 'benign ethnic neutropenia' (BEN). Historically, African ancestry was considered criteria for this diagnosis. However, people of many other ethnicities including people from the Middle East [33] or Crete [34] can have this diagnosis.

Additionally, we now know that lower neutrophil counts seen in many people of African and Arabic descent are strongly associated with the homozygosity of the single nucleotide polymorphism (SNP) rs2814778 located in the promoter region of the Duffy Antigen Receptor for Chemokines (DARC) also named Atypical chemokine receptor 1 (ACKR1) gene [35]. This variant codes the Duffy negative [Fy(a-b-)] blood group. The Duffy positive phenotype is found in only 0.2% of Africans and 99.3% of Europeans [36]. Subsequently, the Duffy null phenotype (Fy(a-b-)) is found in <1% of those with Caucasian or Asian ancestry, but is very common in individuals from Sub-Saharan Africa (80–100%) and the Arabian Peninsula (50–70%) [37]. This geographic distribution is likely the result of positive selection as the Duffy null phenotype is protective against plasmodium vivax. Thus, the Duffy null blood group aligns with the distribution of 'benign ethnic neutropenia.' In fact, the association with the Duffy null blood group and a diagnosis of BEN is very strong ($p = 4.09 \times 10^{-53}$) [38], and there is no additional association between race and neutropenia when accounting for the Duffy null blood group [39]. Notably, the Duffy null phenotype explains only 20–25% of the variation in the neutrophil count between ethnicities [36,39]; therefore, most of the people with the Duffy negative phenotype will not have significantly lower neutrophil counts

Table 3. Main features of non-monogenic chronic neutropenia.

Type of neutropenia with a reference	Age of onset	Context	Diagnosis method	Outcome
Alloimmune [89]	Neonate	Typically very profound neutropenia at birth but no severe infection	Identification of the neutrophil group of the father and mother and alloantibodies in the mother	Recover between 3 and 9 months of age No or few infections related to the neutropenia
Post prematurity neutropenia	Prematurity < 36 weeks	Mild neutropenia No infection Maternal gravidic hypertension	Exclusion of alloimmune neutropenia and context	Recover by end of the first year of life No or few infections related to the neutropenia
Autoimmune neutropenia – primary? Chronic benign neutropenia [27]	Between 6 months and 2 years	Very frequent Profound neutropenia No associated pathologies Can be after community viral infections	Autoantibodies If bone marrow smear, no maturation arrest and sometimes neutrophagocytis [45]	Very limited severe infections Common viral infections are difficult to manage and usually no deleterious consequences Spontaneous recovery after 1 to 6 years
Autoimmune neutropenia – secondary [90]	Young adult	Goujerot Sjorgen syndrome Systemic lupus erythromatosis Rheumatoid disease	Specific autoantibodies	Depending of the underlying disease
Idiopathic immune neutropenia [91,49]	Typically young women	Profound neutropenia Low infection risk	All work up is usually negative In half of them minor sign of biological or clinical auto immunity, like thyroiditis or vitiligo Anti PNN antibodies	No infection, no malignancy Usually chronic
Chronic benign neutropenia associated with Duffy null phenotypes [22,35]	More frequently found in children [22]	No infection Chronic Mild between 0.5 and 1.5 109/L	African origin, frequent Duffy antigen receptor for cytokines null [35]	Chronicity but no infection.
Drug induced neutropenia	Variable frequence according to the type of drugs [92–96]	Usually Profound neutropenia and acute neutropenia following drug exposure Low infection risk	Medical history	Several profile. Sometimes almost acute agranulocytosis Sometimes chronicity but very limited number of infections.

than current reference ranges. In addition, some patients can have lower, clinically insignificant absolute neutrophil counts without the Duffy null phenotype.

The pathophysiology of this neutropenia without clinical sequelae is unclear. Mouse models with the absence of erythroid ACKR1 altered mouse hematopoiesis (including stem and progenitor cells) causing phenotypically distinct neutrophils that readily left the circulation resulting in neutropenia [40]. Proteolytic activity, ROS, and formation of NETs in neutrophils from patients with Duffy null blood group is normal and neutrophil counts in response to lipopolysaccharide (LPS) stimulation were similar in Duffy null and Duffy positive patients despite the lower baseline neutrophil counts in Duffy null patients, which suggest normal neutrophil function and response. Several hypotheses have been put forward: some suggest an excess of migration of circulating neutrophils to tissues like the spleen while others propose a defect of neutrophils release of mature intramedullary neutrophils. Overall, in Duffy null individuals neutrophil function and total body neutrophil count is thought to be normal, but the distribution of neutrophils between blood, tissue, and bone marrow is thought to be different than non-Duffy null subjects [41].

Although this clinically insignificant variant most often seen in those of African descent has historically been called 'benign ethnic neutropenia,' we feel this name is problematic as it implies that ethnicity is causative and that this is a disease that requires intervention [42]. We advocate for an alternative name such as chronic benign neutropenia, Duffy null associated neutrophil count, or typical neutrophil count with Fy (a-b-) status that reflects the genetic underpinning of this variant and highlights that it is not a disease state. Consensus has yet to be reached for an alternative name or expected ranges of normal neutrophil counts. This entity should be considered in patients with isolated chronic neutropenia, without other associated cytopenias, splenomegaly, lymphadenopathy, recurrent infections, or oral damage as well as the absence of secondary or congenital neutropenia. Most individuals with chronic benign neutropenia have neutrophil counts between 0.5 and 1.5 x 10^9/L, but lower figures have been reported especially in the pediatric population underlining that there is currently no clear expected nadir for this population. Despite the mildness of this variant physiology, the patients may undergo to a wide array of expensive and invasive biological tests as well as psychological distress, while searching for a diagnosis. Demargination tests (physical exertion, corticosteroids, adrenaline) do not have a sufficiently good positive predictive value and are not recommended. A careful clinical history and physical exam and evidence of persistence of the neutropenia if available are the best diagnostic tools. Duffy null blood group can be suggestive of this type of neutropenia, but is not a conclusive diagnostic tool as some patients may have clinically insignificant neutropenia without the Duffy null phenotype. Once the diagnosis is confirmed, this entity does not require monitoring or hospital admission. This type of neutropenia does not require any treatment, including no antimicrobial prophylaxis or G-CSF. These individuals are healthy subjects, and are expected to have a lower ANC than current reference ranges without concern for increased infections. The greatest risks are the excess

of precautions and test as well as exclusion from clinical trials, ineligibility for medicines like clozapine, and modified chemotherapy protocols for concern for toxicity from neutropenia [43]. Clear documentation of the benign nature of this variant and alternative ranges for patients with Duffy null phenotype should be pursued to de-classify this as a disease state as well as ensure appropriate medical care for the majority of patients of Arabic and African descent who are Duffy null.

6.3. Primary autoimmune neutropenia of childhood

Autoimmune neutropenia is probably one of the most frequent isolated, chronic, acquired neutropenias diagnosed in infants or toddlers [27,44]. It is diagnosed during the first year of life (median age 8 months, range 3–36 months) and its prevalence is probably underestimated given the mild nature of the condition. Neutrophils can reach very low levels (<0.2 x 10^9/L) that are usually accompanied by mild monocytosis. In addition, the absolute neutrophil count may increase or normalize secondary to bacterial or viral infection. If bone marrow aspiration is performed, the bone marrow is rich with well-represented granulocytic differentiation without evidence of dysplasia and presents a typical picture of neutrophagocytosis [45,46]. Clinically, this entity is usually asymptomatic, but some autoimmune neutropenia may be accompanied by minor infections (most often respiratory) and occasional gingival involvement, or sometimes be discovered in the presence of a serious infection, which will be the only serious infectious episode in the patient. Serum anti-neutrophil antibodies should be tested using several associated techniques, as they have varying specificity and sensitivity. In case of negativity, this search should be repeated to increase sensitivity. The search for fixed antibodies would be more sensitive, but the test is difficult to carry out given the fragility of the cells and not specific. There are also some very rare situations of autoimmune neutropenia in infants associated with more general autoimmune manifestations, but in >95% of cases, this neutropenia remains isolated, well tolerated, and resolves spontaneously before the age of 5 years. In this group, a more limited number of patients may present with persistent neutropenia after 5 years of age, suggesting a more global dysimmunity [47].

6.4. Idiopathic/immune neutropenia of young adults

This entity usually corresponds to a benign condition diagnosed in young adults and has some similarities to both autoimmune neutropenia in children and the so-called ethnic neutropenia. There are three distinguishing features: it occurs in young adults (in practice, from puberty onwards); is usually profound with < 0.5 x 10^9/L [48,49] and can be thought of as a primary autoimmune neutropenia in young adults; is frequently associated with other organ-specific autoimmune diseases (autoimmune thyroiditis, pernicious anemia, etc.). Unlike primary autoimmune neutropenia in children, in adults it is more persistent (usually several years or even life-long) with a female predominance (80% women). Bone marrow evaluation is mandatory to exclude other diagnoses but there is not typical pattern: most of the patients have normal marrow, left deviation or terminal maturation blocking but a few have also hypoplastic granular maturation. In addition, this idiopathic neutropenia is different from chronic neutropenia associated with other autoimmune pathologies [49], such as systemic lupus erythematosus, rheumatoid arthritis/Felty syndrome, Gougerot-Sjögren syndrome [50], Mixed connective tissue disease sometimes associated with LGL [51–53], and those of common variable immunodeficiency [54].

6.5. Congenital neutropenia

Congenital neutropenia is a very heterogeneous group of diseases [16]. These are chronic, hereditary, intermittent, or permanent neutropenias with sometimes very significant variations in the number of neutrophils. They often present during the first year of life and are responsible for recurrent severe and invasive infections. These neutropenias are most often accompanied by oral involvement and chronic periodontal disease (recurrent mouth ulcers, gingivitis and periodontitis that may lead to premature tooth loss and edentulism). The infectious manifestations are diverse (sinusitis, otitis media, angina, pharyngitis, bronchitis), and even severe (pneumonia, bacteremia, septicemia, osteoarticular infection, cellulitis and perineal infection, etc.) [14,55]. A detailed family history should always be obtained. Genetic neutropenias may be associated with extra-hematological abnormalities, directing the clinician to a specific disease (Table 3). The blockage of maturation of the myeloid lineage seen on the bone marrow smear is typical of these conditions, but several genetic entities do not present this maturation arrest and it can be transient in the same patient. Notably, some congenital neutropenias belong to the spectrum of primary immune deficiencies or bone marrow failure syndrome [56]. Table 4 summarizes the different entities described thus far, as well as their mode of transmission and the accompanying hematological and extra-hematological manifestations. Initial presentation in adults, the diagnosis of congenital neutropenia is extremely rare, except for *GATA2* deficiency and *SBDS*.

6.6. Neutropenia of the newborn: peculiarities

The neonatal period is the period of life when the diagnosis of neutropenia is most common [57]. Neonatal viral infections, such as CMV, or bacterial infections, such as streptococcal B infections, are frequently associated with neutropenia [58]. Prematurity, especially after pregnancy-induced hypertension and preeclampsia, may be a cause of neonatal neutropenia. Inborn errors of the adaptive immune system (e.g. CID or SCID or agammaglobulinemia) sometimes include neutropenia. Therefore, immunological assessment is mandatory. Alloimmune neonatal neutropenia is caused by the transplacental transmission of maternal IgG-type antibodies directed against fetal neutrophils. This is an incompatibility between the maternal and paternal granulocytic antigens, which also exists between the mother and the fetus. The mother can then develop, during pregnancy, antibodies directed against the fetal granulocytic antigens, which are inherited from the father. This neutropenia is most often discovered by chance but can be responsible for omphalitis, cellulitis, bacteremia/

Table 4. List of known genetic variants in congenital neutropenia (2021) and the main features.

Subgroup of neutropenia	Gene and disease name (ref)	Ref	OMIM code	Main hematological features	Extra-hematopoietic features	Inheritance and gene localization	Normal function of the gene product/protein
Congenital neutropenia usually without extra-hematopoietic manifestations	*ELANE* Severe congenital neutropenia/cyclic neutropenia	[97,98]	202,700 162,800	Severe and permanent,No maturation arrest, intermittent/cyclic with variable bone marrow features		Dominant 19q13.3	Protease activity Antagonism with alpha 1 antitrypsin
	CSF3R Germline mutation of CSF3R	[99]	202,700	Permanent maturation arrest, unresponsive to G-CSF	No	Dominant 1p35-p34.3	Transmembrane G-CSF receptor/intracellular signaling
	WAS Severe congenital neutropenia	[100]	301,000	Severe permanent, maturation arrest, monocytopenia	No	X-linked Xp11.4-p11.21	Cytoskeleton homeostasis
	CXCR2 chronic neutropenia	[101]		Severe permanent, no maturation arrest, myelokathexis	No	Recessive 2q35	Chemokine receptor (CXCL12)
	SEC61A1	[102]		No maturation arrest	No	Recessive 3q21.3	The translocon is a complex of protein which transports nascent polypeptides with a targeting signal sequence into the interior space of the endoplasmic reticulum
	SRP 54	[103]		Maturation arrest	Mostly no, but some mutations are associated with Exocrine pancreas deficiency, mental retardation	Dominant 14q13.2	The signal recognition particle (SRP) is a protein-RNA complex) that recognizes and targets specific proteins to the endoplasmic reticulum . SRP54 and SRP68 are one protein of this complex
	SRP68	[104]		Maturation arrest	No	Recessive 17q25.1	
Congenital neutropenia with frequent extra-hematopoietic manifestations including innate immunity deficiencies	*SBDS* Shwachman-Bodian-Diamond disease	[105]	260,400	Mild neutropenia, dysgranulopoiesis, mild dysmegakaryopoiesis	Exocrine pancreas deficiency, bone: metaphyseal dysplasia, mental retardation, heart: cardiomyopathy	Recessive 7q11.22	Ribosomal protein Regulation of RNA expression
	EFL1 syndrome	[106]	260,400	Mild neutropenia, dyserythropoiesis	Exocrine pancreas deficiency, bone: metaphyseal dysplasia, mental retardation	Recessive 15q25.2	Ribosomal protein Regulation of RNA expression
	GATA2 syndrome	[107]	614,038 614,172	Mild neutropenia, monocytopenia, macrocytosis	Lymphedema, deafness, mycobacteria HPV infections	Dominant 3q21.3	Transcription factor
	*G6PC3*Severe congenital neutropenia	[108]	202,700	Maturation arrest	Skin-prominent superficial venous network, heart: atrial defect, uropathy	Recessive 17q21	Glucose 6-phosphatase complex catalytic unit
	*SLC37A4*Glycogen storage type Ib	[109]	232,220	No maturation arrest	Hypoglycemia, fasting hyperlactacidemia, and glycogen overload of the liver	Recessive 11q23.3	Glucose 6-phosphatase complex trans ER transporter
	TAZ Barth disease	[110]	302,060	No maturation arrest	Hypertrophic cardiomyopathy, myopathic syndrome, 3-methyl glucaconic aciduria	X-linked Xq28	Tafazzin, phospholipid membrane homeostasis
	CXCR4 WHIM syndrome	[111]	193,670	Severe permanent, no maturation arrest, myelokathexis	Lymphopenia, thrombocytopenia, Cardiopathy type Tetralogy of Fallot	Dominant 2q21	Chemokine receptor (ligand CXCL12)
	JAGN1 Severe congenital neutropenia	[112]	616,022	Variable	Bone abnormalities, exocrine pancreatic enzyme	Recessive 3p25.3	ER protein
	VPS13B Cohen syndrome	[113]	216,550	No maturation arrest	Psychomotor retardation, clumsiness, microcephaly, characteristic facial features, hypotonia and joint laxity, progressive retinochoroidal dystrophy, myopia	Recessive 8q22-q23	Sorting and transporting proteins in the ER

(*Continued*)

Table 4. (Continued).

Subgroup of neutropenia	Gene and disease name (ref)	Ref	OMIM code	Main hematological features	Extra-hematopoietic features	Inheritance and gene localization	Normal function of the gene product/protein
	GFI1 Severe congenital neutropenia	[114]	202,700	Permanent/severe or mild, sometimes maturation arrest	Internal ear (in mouse model), lymphopenia	Dominant 1p22	Transcription factor Regulation of oncoprotein
	HAX1 Kostmann's disease	[115,116]	202,700	Maturation arrest	Central nervous system: mental retardation/ seizures	Recessive 1q21.3	Anti-apoptotic protein located in the mitochondria and cytosol
	AP3B1 Hermansky – Pudlak syndrome type 2	[117]	608,233	No maturation arrest	Albinism	Recessive 5q14.1	Cargo protein/ER trafficking with ELANE interaction
	LAMTOR2 Chronic Neutropenia	[118]	610,389	No maturation arrest	Albinism	Recessive 1q21	Lysosome packaging
	USB1 Poikiloderma type Clericuzio	[119]	604,173	No maturation arrest, minor dysgranulopoietic features	Skin: poikiloderma	Recessive 16q21	Not known
	VPS45 Severe congenital neutropenia	[120]	615,285	Maturation arrest/ myelofibrosis	Nephromegaly, hepatosplenomegaly, mental retardation	Recessive 1q21.2	Role in segregation of intracellular molecules into distinct organelles
	TCIRG1 Severe congenital neutropenia	[121]	202,700	Variable	Skin angiomatosis	Dominant 11q13.2	
	*EIF2AK3*Wolcott-Rallison syndrome	[122]	604,032	Maturation arrest	Insulin-dependent neonatal diabetes	Recessive 2p11.2	ER stress
	*CLPB*syndrome	[123,124]	616,254	Maturation arrest	Mental retardation, congenital cataract, 3-methyl glucaconic aciduria	Recessive 11q13.4	
	STK4 (*MST1*) syndrome	[125]	614,868	Intermittent neutropenia/auto immune neutropenia	Atrial defect	Recessive 20q13	Serine/threonine protein kinase
	SMARCD2	[126]		Dysplastic syndrome, no granule in neutrophil	Chronic diarrhea, bone abnormalities, low set ears	Recessive 17q23	
	SASH3	[127]		Maturation arrest	Auto immunity and viral infection	X-linked Xq26	
	CARD 11	[128]		Maturation arrest and hyperlymphocytosis	Skin disorders	Dominant 7p22.2	
	Pearson syndrome	[129]	557,000	Vacuolization of marrow precursors and a Perl's staining revealing ring sideroblasts	Pancreatic insufficiency, commonly, anemia and thrombocytopenia, usually later in life neurological delayed is presente with Kearns-Sayre syndrome Elevated lactate: pyruvate ratio	Complex inheritance	Deletion in mitochondrial DNA

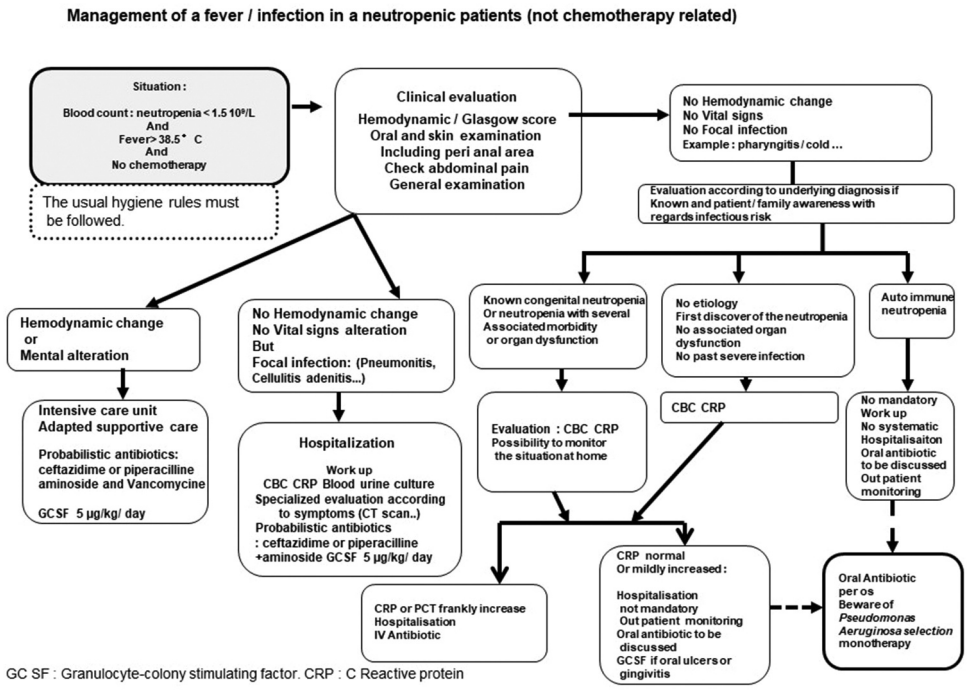

Figure 2. Management of fever or infection in a patient with non-chemotherapy neutropenia.

Management of fever or infection in a patient with non-chemotherapy neutropenia.

sepsis, and meningitis. Lastly, maternal idiopathic/immune neutropenia may transmit granulocyte antibodies, which may be responsible of a neutropenia in her newborn, being responsible of a profound, but transient neutropenia [59]. Maternal antibodies disappear after 3 months of life, but neutropenia can persist until 6 months of age [60]. Congenital/inherited neutropenia (i.e. monogenic) can be diagnosed in a newborn, but the incidence of these neutropenias at birth remains modest at approximately 30 patients out of 1×10^6 births, whereas 1–3% of newborns are currently considered to be neutropenic regardless of the underlying cause [24].

7. Supportive care

7.1. Neutropenia, infections and emergency

The discovery of an infection or fever in a neutropenic patient raises concerns. Recommendations for the management of infections are often applied in neutropenic patients in the context of chemotherapy, and hospitalization and intravenous antibiotic therapy are then considered standard. It is important to have a more personalized approach apart from neutropenia secondary to chemotherapy (Figure 2). The onset of fever, regardless of its severity, may suggest the presence of a potentially fatal bacterial infection requiring adequate antibiotic therapy (Staphylococcus aureus and Gram-negative bacilli, including Pseudomonas). However, the vast majority of febrile episodes observed in neutropenic patients, including severe congenital neutropenia, are of viral origin and resolve spontaneously. In contrast to management of neutropenia with febrile episodes in cancer patients, treatment decision may be more dependent on individual factors including clinical examination and blood tests such as Complete blood count, CRP, or Procalcitonine (Figure 2). If the patient presents with altered mental status, hemodynamic instability, or a focal infection (cellulitis, pneumonia, colitis, etc.), hospitalization is typically required and antibiotic treatment should be started immediately after samples for microbiological analysis (blood cultures, samples from skin lesions, peripheral samples) have been obtained. Empiric intravenous antibiotic therapy should aim to cover Gram-positive cocci and Gram-negative bacilli, such as ceftazidime, piperacillin-tazobactam, or imipenem combined with an aminoglycoside (considering local preferences for rational use of antibiotics). Of course, impaired hemodynamics and septic shock make admission to an intensive care unit essential. In the event of hospitalization, specific isolation measures are not mandatory. The usual hygiene rules must be followed. Special attention should be paid to skin involvement, especially in the perineal region. Characteristically, skin involvement can manifest as painful local inflammation without the appearance of pus (due to lack of neutrophils), progressing to local necrosis with slow healing (accentuated by functional neutrophil defects). G-CSF should be prescribed in such an episode. Although not supported by controlled clinical trials, transfusions of allogeneic neutrophil granulocytes may be beneficial in very few cases. It is always desirable to approach a hematology service to discuss short – and long-term therapeutic management.

7.2. Prevention of infections

The etiology of neutropenia remains key to organizing patient care. In most genetic diseases, an interdisciplinary approach is mandatory. Prevention of infections in chronic neutropenia

patients is necessary. However, the indication for prophylaxis depends on a personalized assessment of the risk of infection, personal history, and the extent and type of neutropenia.

Prophylactic antibiotic therapy (sulfamethoxazole/trimethoprim taken once daily orally at a daily dose of 30 mg/kg/day sulfamethoxazole) is one potential option. However, continuous use of broad-spectrum antibiotics raises concerns with respect to emergence of resistant bacteria. This is more worrisome than the rare incident of sulfamethoxazole/trimethoprim associated neutropenia. This treatment does not prevent the chronic gingivitis which justifies regular dental follow-ups as well as good oral hygiene. In the absence of lymphoid deficiencies, prophylactic drugs preventing mycotic or viral infections are not indicated. Granulocyte growth factor or G-CSF has proven valuable in reconstituting neutrophil counts. This medication is administered subcutaneously. Several forms are marketed: filgrastim (NEUPOGEN®, ZARZIO®, or NIVESTIM®) and lenograstim (GRANOCYTE®). The starting dose is typically 3–5 ug/kg once daily for a period of 14 days. The maintenance dose is adjusted according to the clinical and biological response. In the event of clinical improvement (absence of infections and oral involvement), the interval can be extended to every 3 days. In the event of a poor clinical response, the clinician may need to increase the dose (in steps of 3–5 µg/kg) or shorten the interval between injections (up to a daily injection). The effectiveness of these changes should be evaluated after a minimum of 2 weeks. If bone pain occurs, the dose should be reduced rapidly. There are no real predictors of the G-CSF response and tolerance, but acquired causes (autoimmune or idiopathic neutropenia) generally respond to very small doses, whereas genetic causes sometimes may require high doses [13,61,62]. A patient is considered a non-responder if the required dose of G-CSF is >50 µg/kg/day and a high-threshold responder if the dose of G-CSF is between 10 and 50 µg/kg/day. The goal of treatment is to sustain a sufficient neutrophil number (e.g. > 1 x 10^9/L) and a satisfactory clinical condition that allows the patient to lead a normal life. Once the appropriate dose for the patient has been reached, biological monitoring can be carried out with a CBC every 4 months (3 times/year). The most common side effects are bone pain, myalgia, and headache, which are due to excessive bone marrow stimulation. Beyond its quantitative effect on neutrophils, G-CSF also improves the function of the latter; it increases their bactericidal power by stimulating the oxidative function associated with phagocytosis. G-CSF acts on myeloid cells only and therefore does not alleviate non-hematological co-morbidities. Of note, patients with defined congenital neutropenia syndromes are at marked risk of developing myelodysplastic syndrome or acute myeloid leukemia. It has been described most often with *ELANE* neutropenia, *HAX1*, and Shwachman-Diamond syndrome, as well in *GATA2* syndrome [5,6,11,63]. This risk may be aggravated by the use of high doses of G-CSF. Therefore, it is advisable to use G-CSF at the minimal dose required for an adequate quality of life.

In view of the risk of clonal outgrowth and MDS/AML, repeated bone marrow examination is advisable to exclude the appearance of clonal genetic mutations (and/or chromosomal abnormalities). associated with hematologic malignancies is also recommended in congenital neutropenia. Notably, the clonal evolution from birth appears to be driven by the germline variant [64], with typically a *CSF3R*and *RUNX1* clone in *ELANE* neutropenia [65,66], *TP53* and *eiF6* clone in Shwachman diamond syndrome [8,67], and connexin mutations in *GATA2* [68]. These molecular changes are considered pre-leukemic conditions and warrant consultation with an experienced HSCT team.

7.3. Specific treatments in some congenital neutropenia

In the last 3 years, new molecules have been adapted to the pathophysiology of the three genetic diseases and are now in clinical trials or evaluation. In *CXCR4* WHIM syndrome, a CXCR4 subcutaneous inhibitor (plerixafor) has been shown to be efficacious [69,70] and is also proceeding in a clinical trial with mavorixafor, an oral compound [71]. Significant progress has also been made in glycogen storage disease type Ib and *G6PC3* – (glucose-6-phosphatase catalytic subunit 3) deficiency neutropenia, which are related to a defect in the glucose-6-phosphatase enzyme. The mechanism of the neutropenia in both of these diseases was recently elucidated. In neutrophils, the transporter G6PT and the phosphatase G6PC3 collaborate to metabolize 1,5-anhydroglucitol-6-phosphate (1,5AG6P), a phosphorylated analogue of glucose that otherwise accumulates into the neutrophils from these patients and intoxicates them due to powerful inhibition of the glucose phosphorylating enzyme hexokinase [72]. Therefore, G6PT transports not only glucose-6-phosphate, but also its structural analogue 1,5AG6P (i.e. 1,5-anhydroglucitol-6-phosphate), which is dephosphorylated by G6PC3 in the endoplasmic reticulum in 1,5AG (i.e. 1,5-anhydroglucitol), preventing its accumulation in neutrophils. When either G6PT (GSDIb patients) or G6PC3 (G6PC3-deficient patients) are deficient, 1,5AG6P accumulates in the neutrophils [72]. Modulating the concentration of 1,5AG in the blood of G6PC3-deficient mice [73] impacts the number of neutrophils. The precursor of the toxic metabolite (1,5-AG) is filtrated and then reabsorbed by sodium-glucose co-transporter (SGLT2). SGLT2 inhibitors, such as empagliflozin or dapagliflozin, which are commonly used clinically as anti-diabetic drugs to treat type 2 diabetes, inhibit the SGLT2 transporter and hence reabsorption of 1,5-AG and thus decrease the concentration of the toxic metabolite in the body [72]. These findings have a potential clinical impact because they allow, in G6PT – and G6PC3-deficient patients, the reversal of clinical manifestations of neutropenia and neutrophil dysfunction, as recently confirmed in four patients with GSDIb [74].

7.4. Allogeneic hematopoietic stem cell transplantation (HSCT)

Before the era of G-CSF, allogeneic HSCT was the only curative treatment for severe congenital neutropenia. The currently validated indications for HSCT in congenital neutropenia are: non-response to G-CSF, clonal evolution with acute myeloid leukemia/myelodysplastic syndrome or molecular or

cytogenetic marrow evidence of a pre-leukemic state, the occurrence of refractory pancytopenia, and long-term use of high doses of G-CSF (>15 µg/kg/day) [13,75]. In patients with *GATA2* deficiency, HSCT should strongly be considered in the case of severe immune deficiency or alveolar proteinosis.

7.5. Other aspects: vaccination, hygiene rules, isolation, diet

Several case series have reported osteopenia, or even early osteoporosis, in 40% of patients followed for congenital neutropenia [76,77]. It appears to be independent of the genetic type of neutropenia in question. Genotype-phenotype correlation studies are still necessary in order to better characterize individuals at risk and offer them a means of prevention. We must remember the danger of intramuscular injections and rectal temperature measurements. Most vaccines, including live viral vaccines, can be used in the majority of neutropenia, with the exception of the rare neutropenia associated with complex immune deficiency. They are even desirable.

No dietary restriction is necessary in neutropenic children. Childcare facilities may be attended by neutropenic children. They are not specifically susceptible to viral epidemics and there is no reason to deprive them of these opportunities for social interaction.

7.6. Pregnancy

The number of women with congenital neutropenia reaching childbearing age is increasing. The use of G-CSF during pregnancy appears to be well-tolerated, with no reported side effects [78]. Genetic counseling should be offered to couples as part of the usual antenatal diagnostic procedures.

7.7. Dental follow-up

Chronic neutropenia, regardless of its cause, but especially congenital neutropenia, predisposes the patient to oral lesions, including aphthous ulcers, gingivitis, periodontitis, and enamel disorders (particularly in Shwachman diamond syndrome). Each person with chronic neutropenia has their own oral disease profile, but all are frail, sometimes with major deterioration in quality of life. Basic care that is easy and affordable is recommended, but a large number of situations require specialized periodontal follow-up. Regular and meticulous tooth brushing should be done twice a day with fluoride toothpaste. Dental follow-up is essential, in addition to follow-up by the referring doctor, and should be regular (2 to 4 times a year depending on the oral condition). It concerns children and adults and may be implemented as soon as the first teeth appear. It is important to preserve the deciduous dentition, to allow normal masticatrory function and harmonious eruption of the permanent teeth. Regular periodontal care including scaling is recommended The use of dental implants is not recommended due to the high risk of jaw bone infections, but exceptions can be made after discussion and collegial decision. In regards to dental braces and orthodontic treatments, they are generally very poorly supported and not recommended. The frequency of periodontitis and resulting tooth loss, which is observed in most of the types of congenital neutropenia, is close to that found for other phagocyte disorders [79], such as leukocyte adhesion deficiency (LAD) [80] and Papillon–Lefevre syndrome (PLS) [81]. These observations suggest interest in a therapeutic approach mediating inflammation, such as cathepsin inhibitors [82] for PLS or interleukin-12 or −23 blockade for LAD [83].

7.8. Quality of life

Treatment with G-CSF has significantly improved the quality of life of patients with congenital neutropenia [84]. The majority of children who are treated are able to lead a normal life (nursery, school, community life, sports, group games, etc.). Understanding the disease and coping with its various aspects is essential for patients. This allows better compliance with treatments and medical monitoring. The advantage of centralizing patient monitoring through a national registry allows for consistent medical care. This grouping also aims to better describe the different genetic entities and to offer patients new avenues of treatment. Finally, the exchange within the framework of patient associations creates the possibility for patients to share their personal experiences [85].

8. Conclusion

Neutropenia is common in medical practice. The diagnostic process starts with analyzing the context of its discovery and collecting some key information on the potential seriousness of the situation. The association with an impairment in several blood lines and the presence of a severe infection (sepsis or deep infection) leads to both an urgent specialized assessment and appropriate antibiotic therapy. In the majority of cases, we do not find such an emergency and start a monitoring period of a few weeks; most cases of neutropenia are transient. If the situation persists, a more complete assessment is offered that aims to establish an etiological diagnosis. The most frequent causes are 'ethnic' (best named chronic benign neutropenia), 'autoimmune,' and more rarely congenital neutropenia. Neutropenia in and of itself should not lead to restrictions in social life, but chronic, severe neutropenia may justify prophylaxis for infections using long-term antibiotic therapy or G-CSF therapy.

9. Expert opinion

Neutropenia is very easy to detect in the blood count and is a relatively frequent finding in both pediatric and adult patients. When neutropenia is observed, physicians should first detect the critical situations associated with this biological abnormality. Such situations are not necessarily associated with a very low absolute neutrophil count (< 0.5 x 10^9/L), and even low absolute neutrophil counts can be completely harmless. Critical situations [25] are associated with:

*Bacterial infections, regardless of site (skin, subcutaneous infection including cellulitis, adenitis, pneumonitis, deep infections such as liver abscess, oral infections such as gingivitis, aphthosis, or paradontopathies);

*Additional hematological abnormalities, such as anemia or thrombocytopenia;

*Associated malformations or organ dysfunction.

If one such critical situation is present or the neutropenia is chronic, lasting more than 3 months, a specialized hematological consultation should be organized quickly. The vast majority of isolated neutropenias are transient, most often secondary to a viral or bacterial infection and less commonly with malignant hematological disease. Chronic neutropenia can be based on several etiologies, including 'ethnic' neutropenia, autoimmune neutropenia in young children, idiopathic/immune neutropenia in young adults, and the rare genetic neutropenia.

Because of its prevalence, progress is expected in the characterization of 'ethnic' neutropenia. This form of neutropenia is statistically associated with African origin and the Null Duffy phenotype of red blood cells [35]. However, these two characteristics are not enough to define such a clinically benign entity. Most of the people bearing the Null Duffy phenotype and individuals of African origin are not neutropenic, and other geographic areas can be concerned with this 'chronic benign neutropenia' [42]. Progress will not be in the definition of a new morbid entity, but in reassuring physicians who find such a neutropenia. Such situations do not need extensive evaluation and patients with such a neutropenia can safely receive a cytostatic drug for an intercurrent disease [42,86].

In contrast, monogenic neutropenia, which represents an extreme minority of patients with neutropenia, needs progress.

The first progress expected is better classification for all such patients. Determining the gene responsible of the disease is an important medical achievement. Approximately 30 genes are now known [16], and the screening of such a panel of known genes can be done easily with targeted next generation sequencing. However, it remains a group of patients with chronic neutropenia associated with severe medical consequences and clinical manifestations occurring early in infancy, without identification of any morbid gene. Such unclassified congenital neutropenia warrants genetic research in order to identify the genetic causes.

The second progress expected in this area is the constitution of the cohort of patients. Such diseases are extremely rare. Without registry and prospective follow-up of the patients (i.e. without a well-structured cohort), major information is missing. Their natural history, their short-term and late-term complications, and the leukemia outset are key information to offer such patients the best outcome as possible and to evaluate present and future therapies. Some registries exist and should be extended and reinforced [4,5].

Pathophysiology: Gene determination offers diagnosis and characterization of the disease but, in many diseases, the path from the gene abnormality to the disease remains elusive. Understanding the biological steps leading from a punctual mutation to an abnormally functioning protein and later to organ dysfunction, almost in a mechanistic way, is a major aim in this field because it may pave the way for specific therapy.

Therapy: The range of therapies available in the area of chronic neutropenia is broad. GCSF has been used for 25 years and, given in a cautious way, is still a very powerful therapy. In case of refractoriness to GCSF or complications, such as myelodysplasia, HSCT remains indicated in a more reliable way. However, some new approaches should be mentioned:

Mobilization of the myeloid cells by CXCR4 inhibitor: This is made possible by the identification of gain of function (GOF) in CXCR4 in WHIM syndrome. CXC4R gain of function is responsible for cell retention and both neutropenia and lymphopenia. CXCR4 inhibitors (plerixafor, and more recently mavorixafor) have been shown to antagonize the GOF of the CXCR4 mutant protein and are on the way to being patented in this disease [71]. Extension of CXCR4 inhibitors to other neutropenias has to be evaluated in the future.

Detoxification: Glycogen storage disease type Ib and glucose-6-phosphatase catalytic subunit 3 (G6PC3) neutropenia are extremely rare neutropenias. Their mechanisms were recently elucidated. In neutrophils, the transporter G6PT and phosphatase G6PC3 collaborate to metabolize 1,5-anhydroglucitol-6-phosphate (1,5AG6P), a phosphorylated analogue of glucose that otherwise accumulates in the neutrophils of these patients and intoxicates them due to powerful inhibition of the glucose-phosphorylating enzyme hexokinase [72]. Modulating the concentration of 1,5AG in the blood impacts the number of neutrophils. The precursor of the toxic metabolite (1,5-AG) is filtered and then reabsorbed by sodium-glucose co-transporter (SGLT2). SGLT2 inhibitors, such as empagliflozin or dapagliflozin, which are commonly used clinically to treat type 2 diabetes, inhibit the SGLT2 transporter and reabsorption of 1,5-AG, decreasing the concentration of the toxic metabolite in the body and restoring the neutrophil function and number [74].

Somatic genetic rescue (SGR), i.e. somatic genetic modifications that fully or partially counteract the deleterious effects of germline mutations, thereby providing a selective advantage to the unmodified cells: SGR has been detected in some Mendelian hematopoietic diseases [87]. In rare cases of such inherited diseases, SGR has been shown to substantially temper patients' clinical features and sometimes even completely cure the disease [88]. More recently, somatic genetic events in EIF6 (including interstitial chromosomal deletion, reciprocal translocation, and point mutations) that either sharply decrease eIF6 production or affect its function have been demonstrated to represent another type of SGR in SDS patients [8,88].

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