# Inborn Neutrophil Disorders: A Unique Case of Chronic Granulomatous Disease and a Review of the Literature

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**ABSTRACT** Neutrophils serve as a cornerstone of innate immunity. Beyond their classical antimicrobial repertoire, these cells are versatile and capable of shaping the adaptive immune response through direct interactions with dendritic cells and lymphocytes in addition to cytokine-mediated effects. Additional functional phenotypes have also been described with regard to cancer and chronic inflammation. The clinical importance of neutrophils in host defense is perhaps best illustrated by the spectrum of inborn neutrophil disorders, ranging from congenital neutropenia to defects of adhesion and phagocytosis. We present a patient with clinical and laboratory features of hemophagocytic lymphohistiocytosis with a bacterial infection. The patient was subsequently found to carry a homozygous variant in the NCF2 gene, establishing a diagnosis of autosomal recessive chronic granulomatous disease (CGD). This presentation, combining cytokine storm with ongoing infection-driven inflammation, exemplifies the multifaceted role of neutrophils in health and disease. In this review, we provide clinical and immunological insights into neutrophil disorders, illustrated through a case of CGD as a paradigm of primary neutrophil dysfunction.

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**KEY WORDS:** chronic granulomatous disease (CGD), inborn errors of immunity (IEI), neutrophils, innate immunity

Neutrophils are hematopoietic cells that originated from the bone marrow and are a key player in innate immunity [1]. They fight invasive infections and are a part of immune regulation and tissue healing. At the affected tissues, neutrophils display an impressive array of antimicrobial functions, including degranulation, production of reactive oxygen species (ROS), phagocytosis, and formation of neutrophil extracellular traps (NETs) [1]. Neutrophils are much more complex cells with effector functions in the innate immune response as well as the capacity to modulate the adaptive immune response via direct interaction by producing cytokines that affect dendritic cells and lymphocytes [1]. In addition, a different functional phenotype has been recently described, particularly in cancer and inflammation [1]. Deficiency or insufficiency of a specific cell can indicate its role in host defense. For example, inborn neutrophils disorders constitute a wide spectrum of diseases from congenital neutropenia to dysfunctional adhesion or phagocytosis, which demonstrates their cardinal place in host immunity.

We recently evaluated a patient who presented with preliminary symptoms of clinical and laboratory hemophagocytic lymphohistiocytosis (HLH) syndrome due to bacterial infection. She was later diagnosed with homozygous variants in the *NCF2* gene, causing autosomal recessive chronic granulomatous disease (CGD). This example of cytokine storm and ongoing inflammation due to infection demonstrate the many faces of neutrophils function. The purpose of this review is to provide clinical and immunological insights on neutrophil disorders in general and by presenting a case of neutrophil defect disorder such as CGD.

## CLINICAL DESCRIPTION AND REVIEW OF THE LITERATURE

The patient was referred to our institution at 2.5 years of age with a suspected diagnosis of HLH syndrome. The 2024 revised HLH criteria involved either a known genetic mutation for familial HLH (FHL), abnormal lymphocyte cytotoxicity assays, or meeting 5 of 7 clinical/lab findings, including fever, splenomegaly, cytopenias (at least two lineages), hypertriglyceridemia or hypofibrinogenemia, hemophagocytosis, elevated Ferritin levels, and

elevated soluble CD25. She was born after a normal pregnancy to two healthy first-degree consanguineous parents and had no other siblings. At the age of 6 months, she presented with cervical lymphadenitis that was treated in a conservative manner. A few months later she underwent surgical drainage of a different skin abscess, which was located near the vaccination site of her previous live attenuated *BCG* vaccine. She also two episodes of acute otitis media. Otherwise, she was healthy and developed normally. Prior to her diagnosis, she was hospitalized due to prolonged fever, bi-cytopenia (hemoglobin of 6 g/dl), platelet count of 40 k/microL, normal neutrophil count, elevated liver enzyme, and remarkable elevated ferritin. Her blood culture grew *Salmonella typhi* and *Enterococcus* and the bone marrow examination was suggestive of hemophagocytosis. Further immunologic investigation revealed normal immunoglobulins levels, normal lymphocyte immuno-phenotyping, other than increased percentage of $CD38^{+}HLADR^{+}$ of 35% (gated on $CD8^{+}$ cells) as a marker for acute persistence T cell activation. These cells expressed high levels of the activation markers CD38 and HLA-DR, suggesting they were a subset of CD38high/HLA-DR+CD8+ T cells, as well as of the activation/exhaustion markers CD25, PD1, CD95, and interferon-γ. High expression of these cells is associated with HLH [2].

**NEUTROPHIL DISORDERS ENCOMPASS A BROAD SPECTRUM OF CONGENITAL AND ACQUIRED ABNORMALITIES THAT IMPAIR HOST DEFENSE AND PREDISPOSE TO SEVERE BACTERIAL AND FUNGAL INFECTIONS AS WELL AS IMMUNE DYSREGULATION.**

Soluble IL-2 receptor level was also elevated with values > 2580 (U/ml). All this was appropriate with the diagnosis HLH. Due to recurrent invasive infection with typical pathogen, CGD was suspected and a dihydrorhodamine test was performed. The latter is a key diagnostic blood test for CGD, which measures the oxidative burst of neutrophils, helping to confirm a CGD diagnosis and sometimes identifying the specific type of CGD or carrier status. In our case, results were abnormal with severely reduced neutrophils response to PMA (1%) and *E. coli* (1%). Secondary causes for immunodeficiency were excluded. Due to familial consanguinity, a homozygous CGD recessive disease trait was suspected and a genetic analysis by whole exome sequencing identified a rare bi-allelic homozygous mutation in the *NCF2* gene (c.1171_1175del; p. Lys391Glufs Ter9 Exon 12/15 Frameshift). A variant was considered pathogenic [3]. During her hospitalization she was treated with broad spectrum antibiotics, and all blood cultures were negative. The patient fulfilled the clinical and laboratory criteria for HLH diagnosis in the context of infection in a CGD patient. She started on combined therapy of corticosteroids and etoposide, according to 2004-HLH protocol (published by the Histiocyte society). Later, she became stable, was afebrile and all inflammatory markers were decreased, with normalization of liver enzymes and resolution of the cytopenia. She was referred for a hematopoietic stem cell transplantation, a curative procedure for such patients, and currently is stable with prophylactic antibiotic and anti-fungal therapy and awaits the procedure.

Our case shows the wide clinicopathology spectrum of defects in neutrophil function that display unique and rare complication and via that exhibit their major role in innate and adaptive immunity. HLH is an unusual but important inflammatory complication of CGD. Association between CGD and HLH is well described, mainly due to infectious triggers and even as a presenting symptom of CGD. In addition, it can be an unusual neonatal phenotype of CGD [4]. Of 80 patients diagnosed with CGD, 5 (6.25%) had evidence of HLH. Two children had HLH as the predominant presenting manifestation mimicking the clinical presentation of congenital HLH [5]. In another study, 11 patients (18.3%) fulfilled the HLH diagnostic criteria in a cohort of 60 CGD patients demonstrating a high mortality rate (72.7%) [6]. In some cases, unfortunately, diagnosis of CGD associated HLH was performed only during autopsy [7]. Last, like our case, a 3-year-old boy was diagnosed with HLH secondary to CGD triggered by *Salmonella typhimurium* septicemia [8]. Thus, HLH can be a presenting manifestation of CGD, and workup for CGD should be considered HLH, especially in the setup of infection or inflammation to facilitate early diagnosis and guide management to prevent mortality.

Neutrophil granulocytes are a part of innate immunity. Defects at any stage of this multistep mechanism may compromise immunity, with tendency not only for infections but also inflammation [1]. According to the recent International Union of Immunological Societies update on the classification of human inborn errors of immunity (IEI) [9], there are 45 distinct IEI-associated congenital defects of phagocyte number or function. Neutrophil disorders can broadly be divided into congenital or acquired neutropenia, and functional defects that impair key neutrophil processes including adhesion and rolling, chemotaxis, oxidative burst, and NETosis. Some forms of neutropenia in children, such as benign cyclic neutro-

penia or autoimmune neutropenia of childhood, are relatively common and usually of limited clinical concern compared with the rare congenital neutrophil disorders discussed here.

Neutrophils originate from hematopoietic stem cells in the bone marrow and undergo granulopoiesis. Defects at this stage result in congenital neutropenia syndromes. Mature neutrophils are released into the circulatory system and migrate to sites of infection through process of adhesion and chemotaxis. Impaired trafficking may cause leukocyte adhesion deficiency (LAD) and other motility defects such as Wiskott-Aldrich syndrome. Within the tissue, neutrophils clear pathogen via phagocytosis, ROS generation, degranulation, and neutrophil extracellular trap (NET) formation. Dysfunction of oxidative burst causes chronic granulomatous CGD, while abnormalities in granule formation or release are seen for example in Chediak–Higashi syndrome. Abnormality at any stage compromises host defense and predisposes to recurrent or severe infections [Figure 1].

**FUNCTIONAL NEUTROPHIL DEFECTS CAN MANIFEST WITH HYPERINFLAMMATION SUCH AS HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS EVEN IN THE ABSENCE OF NEUTROPENIA, ESPECIALLY WHEN TRIGGERED BY INFECTION.**

## CONGENITAL/ACQUIRED NEUTROPENIA

Neutropenia is defined as an abnormal low absolute neutrophil count in the peripheral blood, usually below 1500 cells/μL. This value is divided further on to mild (1000–1500 cells/μL), moderate (500–1000 cells/μL), and severe (< 500 cells/ μL) neutropenia [10]. The condition may be acute or chronic. It may be due to infection, bone marrow suppression, immune dysregulation, malignancy, and congenital defects. There are at least 22 different types of congenital neutropenia [9]. Each may have unique characteristics including syndromic features, but all share a common clinical phenotype [Table 1]. It usually presents in early infancy with recurrent bacterial and fungal infections, with bone marrow biopsy showing granulocytic maturation arrest (typically at the promyelocyte/myelocyte stage) [11]. Clinical manifestations may include skin and oropharyngeal infections, recurrent sinopulmonary infections, and deep tissue abscesses. Furthermore, there is an increased risk of osteopenia/osteoporosis and periodontal disease due

**Figure 1.** Developmental, trafficking, and effector functions of neutrophils as well as representative disorders associated with each stage

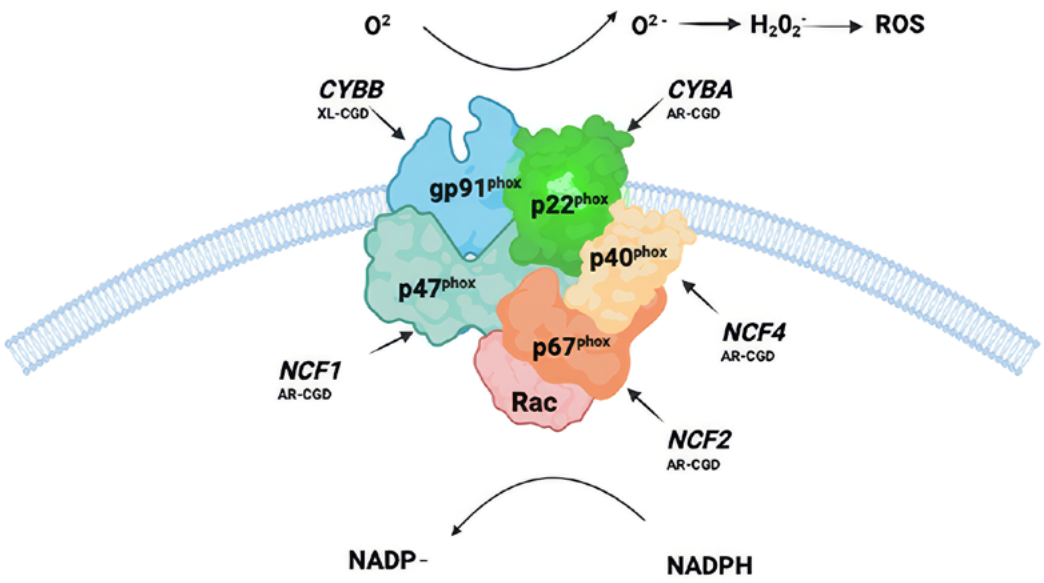


**Table 1.** Congenital defects of phagocyte number; congenital neutropenia disorders, including disease name, causative gene and mode of inheritance, underlying cellular or molecular defect, and additional clinical manifestations

| Type of disease | Gene (Inheritance) | Defect | Associated features |
|---|---|---|---|
| (Elastase deficiency (SCN 1) | *ELANE* (AD) | Myeloid differentiation | Cyclic/congenital neutropenia, susceptibility to MDS/Leukemia |
| GFI1 (SCN2) | *GFI1* (AD) | Myeloid differentiation | Congenital neutropenia B/T cell lymphopenia |
| HAX1 deficiency, Kostman disease (SCN3) | *HAX1* (AR) | Myeloid differentiation | Congenital neutropenia, neurologic defects, susceptibility to MDS/ Leukemia |
| G6PC3 deficiency. (SCN4) | *G6PC3* (AR) | Myeloid differentiation, chemotaxis, $O_2$ production | Congenital neutropenia, congenital heart defect, urogenital abnormalities, deafness, venus angioectasis |
| VPS45 deficiency | *VPS45* (AR) | Myeloid differentiation, and migration | Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly |
| Glycogen storage disease type 1b | *SLC37A/G6PT1* (AR) | Myeloid differentiation, chemotaxis, $O_2$ production | Hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly |
| X-linked neutropenia | *WAS* (XL) | Myeloid differentiation, mitosis | Neutropenia, maturation arrest, monocytopenia, variable lymphoid anomalies |
| P14/LAMTOR2 deficiency | *LAMTOR2* (AR) | Endosomal. biogenesis | Neutropenia, hypogammaglobulinemia, CD8 cytotoxicity, partial albinism |
| Barth syndrome | *TAZ* (XL) | Mitochondrial function | Neutropenia, cardiomyopathy, growth retardation |
| Cohen syndrome | *VPS13B* (AR) | Myeloid differentiation | Neutropenia, dysmorphism, mental retardation, obesity, deafness |
| Clericuzio (Poikiloderma with neutropenia) | *USB1*(AR) | Myeloid differentiation | Retinopathy, developmental delay, facial dysmorphism, poikiloderma |
| JAGN1 deficiency | *JAGN1* (AR) | Myeloid differentiation | Maturation arrest, osteopenia |
| 3-Methylglutaconic aciduria | *CLPB* (AD/AR) | Myeloid differentiation, mitochondrial protein | Neurocognitive aberration, hypoglycemia, hypotonia, ataxia, seizures, cataract, intra uterine growth retardation |
| G-CSF receptor deficiency | *CSF3R* (AR) | Stress granulopoiesis | No associated systemic features |
| SMARCD2 | *SMARCD2* (AR) | Chromatin remodeling, myeloid differentiation, neutrophil function defect | Neutropenia, developmental delay, myelodysplasia, bone abnormalities |
| CEBPE | *CEBPE* (AR) | Terminal maturation and global dysfunction | Neutropenia poor chemotaxis |
| Schwachman diamond syndrome | *DNAJC21, EFL1* | Neutrophil maturation, chemotaxis ribosomal biogenesis | Pancytopenia, exocrine pancreatic insufficiency |
| HYOU1 deficiency | *HYOU1* (AR) | Unfolded protein dysfunction | Hypoglycemia, inflammatory manifestations |
| SRP54 | *SRP54* (AD) | Protein translocation to ER, myeloid differentiation, neutrophil function defect | Neutropenia E, exocrine pancreatic insufficiency |
| CXCR2 deficiency | *CXCR2* (AR) | Reduced expression of *CXCR2* | Profound neutropenia, myelokathexis, recurrent gingivitis, hyper-gammaglobulinemia |
| DBF4 deficiency | *DBF4* (AR) | Disturbed cell cycle | Neurocognitive developmental aberrations |
| SRP19/SRPRA deficiency | SRP19/SRPRA (AR) | Alteration in neutrophil granulocyte developmental | Neutropenia, exocrine pancreatic insufficiency, growth insufficiency, recurrent pulmonary infections, bronchiectasis |

G-CSF = granulocyte colony-stimulating factor, SCN = severe congenital neutropenia

to bone resorption in the absence or dysfunction of neutrophils that do not inhibit osteoclasts, thereby causing inflammation [11]. Besides infections, some forms of severe congenital neutropenia show a substantially high risk for myelodysplastic syndrome/acute myeloid leukemia over time, with acquiring somatic genetic defects such as monosomy 7 [12]. Most patients manage quite well with daily subcutaneous granulocyte colony-stimulating factor, which may reduce infections; however, some may have refractory disease that requires higher doses or, in severe cases, hematopoietic stem-cell transplantation [11].

### DEFECTS IN NEUTROPHIL MOTILITY

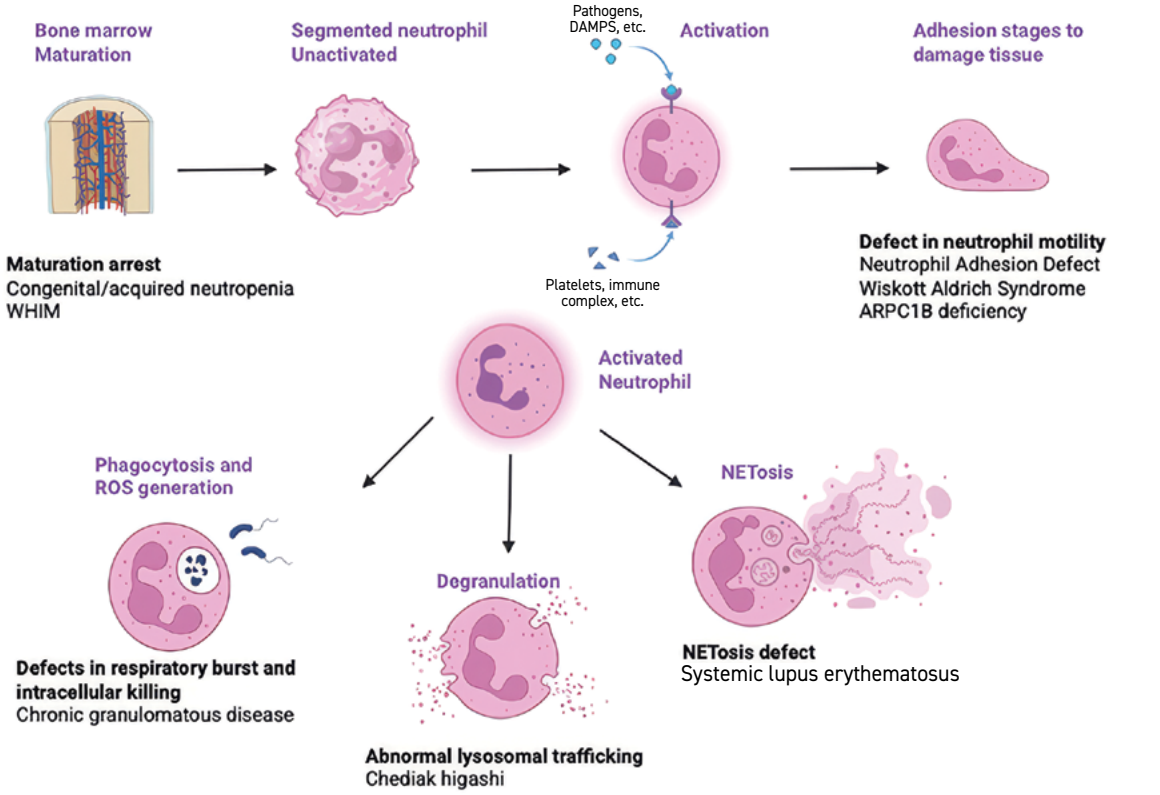
After leaving the bone marrow, granulocytes arrive at the site of infection in a complex process. First, they roll along the vascular endothelium, followed by tight adhesion, crawling, and then transmigration into tissues. This orchestrated process is induced by chemokines, complement components, and bacterial products, which activate receptors upon neutrophil surface [1]. Migration defects may be divided into inherited or acquired abnormalities, which directly affect this well-timed mechanism. Genetic inborn errors of migration include leukocyte adhesion deficiencies (LAD1-3), actin cytoskeleton defects (e.g., ARPC1B deficiency) [13], and other disorders [14]. Acquired defects may be seen in myelodysplastic syndromes due to a reduced, chemotactic response [15]. Another acquired migration defect may be seen in the presence of sepsis, which alters chemokine receptor expression and signaling pathways. These defects increase susceptibility to bacterial and fungal infections [16]. In addition, chronic inflammation may lead to immune dysregulation and autoimmunity.

**EARLY RECOGNITION THROUGH FUNCTIONAL ASSAYS AND GENETIC DIAGNOSIS IS ESSENTIAL TO GUIDE TIMELY TREATMENT, PREVENT LIFE-THREATENING COMPLICATIONS, AND ENABLE CURATIVE OPTIONS SUCH AS HEMATOPOIETIC STEM-CELL TRANSPLANTATION.**

Defects of respiratory burst and in intracellular killing

Neutrophils recognize, consume, and destroy microorganisms, a process called phagocytosis. Recognition is conducted via certain molecular patterns, known as patterns recognition receptors [17]. These receptors on neutrophils bind other patterns known as pathogen-associated molecular patterns [17]. Another way is via immunoglobulin or complement mediated recognition [18]. Post recognition, cytoskeletal rearrangement is induced, and a membrane-bound compartment called the phagosome is created [17]. Within the phagosome ROS is generated via (18) oxidase will induce a hostile environment for en-

**Figure 2.** Structure and activation of the neutrophil NADPH oxidase complex and associated disease-causing genes



gulfed pathogens. Phagosomes may fuse with lysosomes to form a phagolysosome that further facilitates degradation [17]. The process of phagocytosis is essential for innate immunity and homeostasis. Defects in any step (recognition, engulfment, phagosome/lysosome creation, and intracellular killing) may cause susceptibility to bacterial and fungal infections, immune dysregulation (uncontrolled inflammation), and autoimmunity (inability to clear apoptotic cells and particles) [17]. Deficiencies in immunoglobulins or complement proteins may also cause secondary neutrophil function due to reduced ability to recognize and engulf pathogens [18].

The hallmark of a respiratory burst defect is chronic granulomatous disease (CGD), which is caused by pathogenic variants in each one of the subunits of the NADPH oxidase complex. Figure 2 shows the multicomponent NADPH oxidase complex responsible for generating ROS during neutrophil activation. The membrane-bound heterodimer $gp91^{phox}$ (encoded by *CYBB*) and $p22^{phox}$ (*CYBA*) form the cytochrome b_558 core. On cellular activation, the cytosolic regulatory subunits $p47^{phox}$ (*NCF1*), $p67^{phox}$ (*NCF2*), $p40^{phox}$ (*NCF4*), and the small GTPase Rac translocate to the membrane to assemble the active oxidase. Mutations in any component impair electron transfer from NADPH to molecular oxygen, reducing superoxide ($O_2^-$) production and giving rise to CGD [18,19]. There is a total of 5 types of CGD divided by type of inheritance. X-linked CGD, which is the most common form, is caused by variants in *CYBB* which encode the $gp91^{phox}$ subunit of the complex. Other 4 forms are inherited in an autosomal recessive manner, due to variants in *NCF1* (encoding $p47^{phox}$ subunit); *CYBA* (encoding $p22^{phox}$ subunit); NCF2 (encoding $p67^{phox}$ subunit) and NCF4 (encoding $p40^{phox}$ subunit) [19].

Clinically, patients with CGD present with susceptibility to infections with catalase positive bacteria, fungi and mycobacterium. The most common pathogens in CGD patients are *Staphylococcus aureus*, *Burkholderia cepacia* complex, *Serratia marcescens*, *Nocardia*, and *Aspergillus species*, often causing pneumonia, abscesses (liver, skin, lymph nodes), osteomyelitis, and gastrointestinal issues. Other than infections, CGD patients also present immune dysregulation due to uncontrolled and ineffective inflammation [19]. Autoimmunity and inflammatory bowel disease are more prevalent in CGD.

As seen in our index case, HLH may be the presenting symptom in CGD patients, especially in children [20]. Another example is the functional neutrophil defect in Chediak Higashi syndrome, which is caused by pathogenic variants in *LYST* causing abnormal lysosomal trafficking and resulting in the formation of giant granules and defective phagocytosis [21]. Other functional defects have also been described [21]. Other genetic or acquired disorders, and some infections, cause phagosome maturation and fusion abnormality. For example, in lysosomal storage diseases there is an abnormal $Ca^2$ signaling that is crucial for phagosome-lysosomal fusion [22]. *Mycobacterium tuberculosis* inhibits phagosome-lysosomes fusion [23]. Other intracellular pathogens (i.e., *Legionella, Salmonella*) may also have the same effect [24].

#### DEFECT IN NETOSIS

Neutrophil extracellular trap formation (NETosis) is the release of web-like structures which are actually chromatin DNA with histones and antimicrobial particles [25]. NETosis is triggered by different stimuli such as pathogens or immune complexes and is a part of innate immunity. Once activated, a sequence of events takes place and results in NETs entering the extracellular space, which sometimes result in the neutrophil cell death. These NETs help in pathogen neutralizing and clearance and contribute to inflammation and maintain homeostasis [25]. Abnormalities in NETosis is associated in susceptibility to infection, especially extracellular bacteria, autoimmunity, tissue damage and thrombosis [25]. NETosis requires several steps, including actin polymerization and NADPH function [25]. Therefore, in neutrophil defects such as CGD or ARPC1B deficiency (causing actin defect), there is also an NETosis defect component [26]. Immunodeficiency and immune dysregulation is linked to NETosis defect, as seen in systemic lupus erythematosus [27].

#### DISCUSSION

Neutrophil disorders are an important and heterogeneous group of diseases. They represent a significant subset of primary immunodeficiencies, accounting for approximately 5–10% of all IEIs [28]. Defects in neutrophil number or function led to severe, recurrent, and life-threatening infections [29]. Clinically, these defects often present early in life with recurrent, oral ulcers, gingivitis, skin abscesses, pneumonia, and deep-seated infections. Pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida* species raise suspicion for an underlying neutrophil defect [29]. The diagnostic approach to suspected neutrophil defects involves a high level of clinical suspicion according to a patient's medical

history and physical examination. Simple complete blood count with absolute neutrophil count, may reveal neutropenia, and bone marrow aspiration may demonstrate the initial maturation arrest. If normal, both functional and molecular assays should be done, such as DHR testing for chronic granulomatous disease or flow cytometry for adhesion molecule defects. Currently, next-generation sequencing panels targeting genes associated with IEI and specifically in congenital neutropenia, whole-exome sequencing, and whole-genome sequencing are also used. They have been a major diagnostic tool, especially in the decision making regarding hematopoietic stem cell transplantation [30].

## CONCLUSIONS

Neutrophils are an important part of innate immunity, and genetic or acquired defects may cause life-threatening infectious disease and other non-infectious complications. One such complication is the development of HLH in the context of infection in patients with CGD. High clinical suspicion is needed in the absence of neutropenia and when functional defect may be the cause of the clinical presentation. Functional assays such as DHR and genetic diagnostic tools may lead to accurate diagnosis and assist in determining prognosis and guiding tailored therapy. Genetic diagnosis helps broaden an understanding of the spectrum of neutrophil biology and improves comprehension of these rare immune defects.

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Capsule

## Inhaled treprostinil for idiopathic pulmonary fibrosis

**Nathan** and colleagues evaluated the efficacy and safety of inhaled treprostinil in patients with idiopathic pulmonary fibrosis. Building on earlier observations, the investigators assessed pulmonary function, respiratory symptoms, exercise capacity, and quality of life. Treprostinil significantly preserved lung function compared with placebo and delayed disease progression. Patients receiving treatment also demonstrated improvements in respiratory symptoms and several patient-reported quality-of-life measures. The safety profile remained favorable, with no unexpected toxicities. Mechanistic analyses suggested that treprostinil may exert direct antifibrotic effects in addition to its well-established pulmonary vasodilatory properties.

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Eitan Israeli

Capsule

## Setmelanotide for the treatment of acquired hypothalamic obesity

Acquired hypothalamic obesity is a severe disorder that develops following injury to the hypothalamus, commonly after surgery or radiation for craniopharyngioma or other brain tumors. Patients experience uncontrolled hunger, profound weight gain, and marked metabolic dysfunction despite conventional therapies. This randomized clinical trial by **Miller** and co-authors evaluated setmelanotide, a melanocortin-4 receptor (MC4R) agonist, in patients with acquired hypothalamic obesity. Treatment with setmelanotide resulted in significant reductions in body weight, body mass index, and hyperphagia compared with placebo. Patients also showed improvements in metabolic parameters and health-related quality of life. The most common adverse events included nausea, vomiting, injection-site reactions, and skin hyperpigmentation, consistent with previous experience with MC4R agonists.

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Capsule

## Ensartinib in resected ALK-positive non–small-cell lung cancer

Patients with completely resected ALK-positive non-small-cell lung cancer (NSCLC) remain at substantial risk of recurrence despite surgery. In this phase 3 trial, **Yue** et al. evaluated adjuvant ensartinib, a next-generation ALK tyrosine kinase inhibitor. Patients receiving ensartinib experienced significantly longer disease-free survival compared with standard postoperative management. The benefit was observed across multiple patient subgroups and was accompanied by a marked reduction in central nervous system recurrence, an important complication in ALK-positive NSCLC. The treatment was generally well tolerated. Common adverse events included rash, liver enzyme elevations, and gastrointestinal symptoms, with relatively few treatment discontinuations.

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