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# Neutropenia as a Presenting Feature of X-Linked Agammaglobulinemia: A National Multicenter Cohort Study

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## Abstract

# Purpose

Neutropenia is a recognized but incompletely characterized manifestation of X-linked agammaglobulinemia (XLA). To characterize neutropenia as a presenting feature of XLA in a multicenter cohort, describing its severity, clinical presentation, microbiological findings, management, and diagnostic implications.

# Methods

We performed a retrospective multicenter cohort study of 61 XLA patients followed at ten tertiary referral centers in Israel between January 2003 and December 2024. Among patients with neutropenia, we collected and analyzed age at first neutropenia and at XLA diagnosis, absolute neutrophil count (ANC), clinical manifestations and outcomes, isolated pathogens, and treatment with intravenous immunoglobulin (IVIG) and granulocyte colony-stimulating factor (G-CSF).

# Results

Of 61 XLA patients across ten centers, 29 had neutropenia. Median age at diagnosis was 14.5 months (IQR 5.75–24.0) and at first neutropenia was 8 months (IQR 5.0–12.0). Median ANC was 200 cells/μL (IQR 100–600.0); severe neutropenia (ANC < 500 cells/μL) occurred in 21/29 (72.4%). Neutropenia preceded diagnosis in 19/29 patients (65.5%) and coincided with diagnosis or preceded the initiation of IVIG therapy in the remaining 10/29 (34.5%), with a median delay of 6 months (IQR 3–16) among the 17 patients in whom neutropenia clearly preceded diagnosis by more than one month. Pneumonia, skin/soft-tissue infection, fever, and sepsis/bacteremia were most frequent. Four patients (13.8%) received G-CSF; one developed chronic lung disease and one died of Pseudomonas sepsis.

# Conclusion

In this multicenter cohort, neutropenia was a significant presenting feature of XLA and was typically severe. These findings support early evaluation for humoral immunodeficiency, including immunoglobulin levels and B-cell enumeration, in male infants and children presenting with persistent or severe neutropenia, particularly when associated with bacterial infection.

## Introduction

X-linked agammaglobulinemia (XLA) is the most common monogenic inborn error of immunity causing congenital agammaglobulinemia, due to pathogenic variants in Bruton tyrosine kinase (BTK). Impaired BTK signaling arrests B-cell maturation at the pro-B to pre-B cell stage transition, resulting in markedly

reduced or absent peripheral B cells, severe hypogammaglobulinemia, and impaired antibody production. Clinically, affected patients typically present after the decline of maternally derived IgG with recurrent or severe bacterial infections, particularly involving the respiratory tract, skin, bloodstream, and central nervous system.

Neutropenia has been described in XLA but remains under-recognized as an initial manifestation. Published reports have included isolated cases [1, 2], literature reviews [3], and registry-based descriptions [4, 5]. In clinical practice, neutropenia may redirect evaluation toward viral suppression, autoimmune neutropenia, congenital neutropenia syndromes, medication induced, or bone marrow failure, while delaying recognition of an underlying humoral immunodeficiency.

The mechanisms of neutropenia in XLA remain incompletely defined. Proposed explanations include BTK-related effects in myeloid cells, dysregulated inflammatory signaling, impaired Fc receptor-mediated activation, abnormal neutrophil maturation or survival.

The primary objective of this study was to characterize neutropenia as a presenting feature of XLA in a multicenter cohort. We hypothesized that neutropenia represents an under-recognized presenting manifestation of XLA and that it frequently precedes the diagnosis of humoral immunodeficiency. We therefore sought to characterize the timing, severity, clinical presentation, microbiological profile, management, and outcomes of neutropenia in a multicenter cohort of children with XLA.

# Methods

A retrospective national multicenter cohort study was conducted in ten tertiary immunology medical centers in Israel between January 2003 and December 2024. Sixty-one patients with documented X-linked agammaglobulinemia (XLA) were reviewed. The study was approved by the institutional review board at each participating center in accordance with local regulations. The primary objective was to characterize neutropenia as a presenting manifestation of X-linked agammaglobulinemia in a national multicenter cohort. The secondary objectives were to determine the frequency of neutropenia among patients with XLA and to describe its severity, timing relative to XLA diagnosis, associated infectious manifestations, microbiological findings, management, clinical outcomes, and diagnostic delay among patients in whom neutropenia preceded the diagnosis of XLA.

All patients with a diagnosis of XLA who were followed at the participating centers during the study period were included in the national cohort. The diagnosis of XLA was based on a compatible clinical phenotype together with markedly reduced or absent serum immunoglobulins and profoundly diminished or absent circulating CD19 + B lymphocytes, with normal CD3 + T-lymphocyte numbers — an approach consistent with the diagnostic framework subsequently formalized in the 2025 AAAAI/ACAAI/CIS Practice Parameter for the diagnosis and management of inborn errors of immunity [6]. As the study period spanned more than two decades (2003–2024), patients diagnosed earlier in this period predated formal publication of these criteria; such patients were diagnosed according to the standard clinical and immunologic approach in use at the time. A pathogenic *BTK* variant was

documented when molecular testing was available and was used to distinguish XLA from other, non-BTK forms of agammaglobulinemia with a similar phenotype; patients diagnosed before routine molecular testing was available were classified based on their characteristic immunologic phenotype together with a compatible family history.

The 29 patients with documented neutropenia comprised the cohort for the detailed clinical analyses. Patients without documented neutropenia contributed only to the denominator used to estimate the frequency of neutropenia among patients with XLA.

Clinical and laboratory data were extracted retrospectively using a standardized data collection form. Collected variables included demographic characteristics, age at onset of neutropenia, age at XLA diagnosis, absolute neutrophil count (ANC), family history, infectious manifestations, microbiological findings, treatment with intravenous immunoglobulin (IVIG) and granulocyte colony-stimulating factor (G-CSF), and clinical outcomes. For patients in whom neutropenia preceded the diagnosis of XLA, the interval between the first documented neutropenic episode and the diagnosis of XLA was recorded. Longitudinal immunologic parameters, including serial immunoglobulin concentrations, B-cell counts, and *BTK* genotype, were not consistently available and therefore were not included in the analysis.

Neutropenia was defined as an absolute neutrophil count (ANC) below 1,500 cells/μL and was classified according to the lowest documented ANC during the presenting neutropenic episode as severe (< 500 cells/μL), moderate (500–999 cells/μL), or mild (1,000–1,499 cells/μL). This classification follows standard hematologic convention [7]; we acknowledge that normal ANC thresholds vary somewhat with age in infancy. The timing of neutropenia was categorized as occurring before, at, or after the diagnosis of XLA. Diagnostic delay was defined as the interval, in months, between the first documented episode of neutropenia and the diagnosis of XLA among patients in whom neutropenia preceded the diagnosis. Clinical manifestations and microbiologically documented infections were recorded as non-mutually exclusive variables. Data were collected and organized using Microsoft Excel and analyzed using RStudio with R version 4.6.0. Continuous variables are presented as median with interquartile range (IQR) and range or as mean ±

# Results

Of the 61 patients with XLA identified, 29 (47.5%) presented with neutropenia (Table 1). Individual patient-level data are provided in table S1. Median age at diagnosis was 14.5 months (IQR, 5.75–24.0), with a mean of 17.8 ± 14.3 months and a range of 2–52 months. Median age at first neutropenia evaluation was 8 months (IQR, 5.0–12.0), with a mean of 11.0 ± 10.2 months and a range of 2–48 months. ANC was available for all 29 patients (Table 1). Median ANC at presentation was 200 cells/μL (IQR, 100–600.0), with a mean of 361.0 ± 347.0 cells/μL and a range of 0–1300 cells/μL. Neutropenia preceded the diagnosis of XLA in 19/29 patients (65.5%) and coincided with the diagnosis of XLA or preceded the initiation of IVIG therapy in the remaining 10/29 (34.5%); by this definition, neutropenia was documented prior to any immunoglobulin replacement in all 29 patients. Among the 17 patients in whom

neutropenia clearly preceded the diagnosis by more than one month, the median interval to XLA diagnosis was 6 months (IQR 3–16; range 1–38). Three additional patients (patients 2, 4, and 8) were classified as preceding diagnosis despite a very short apparent interval: in two of them (patients 2 and 4), neutropenia was documented only two weeks and one month, respectively, before the diagnosis of XLA, and in the third (patient 8) the diagnosis of XLA was made on the basis of a family history of XLA rather than because the patient was clinically unwell; in all three, neutropenia was confirmed before IVIG was started. Clinical manifestations of the neutropenic patients (Table 2) included: (individual patient-level presentation, pathogens, and treatment are provided in table S2) pneumonia or pleuropneumonia was documented in 10/29 patients (34.5%), skin or soft tissue infection in 10/29 (34.5%), fever or neutropenic fever without a focus in 9/29 (31.0%), and sepsis or bacteremia in 6/29 (20.7%). Two patients (6.9%) were identified through family history screening. Pseudomonas aeruginosa infection was identified in 7/29 patients (24.1%), including one patient with both pneumococcal and Pseudomonas infection. Haemophilus influenzae was documented in 2/29 (6.9%), Streptococcus pneumoniae in 2/29 (6.9%), Salmonella in 1/29 (3.4%), adenovirus in 1/29 (3.4%), and Giardia in 1/29 (3.4%). Three patients had infections involving more than one pathogen (Table 3). All patients in the study received IVIG. Four patients (13.8%) with severe neutropenia (ANC ≤ 100 cells/μL in all four) received G-CSF. One patient (3.4%) developed chronic lung disease, and one patient (3.4%) died of Pseudomonas sepsis.

Table 1
Baseline characteristics

| **Variable** | **Value** |
|---|---|
| XLA patients | 61 |
| Patients with XLA and neutropenia | 29 (47.5%) |
| Age at diagnosis, months, median (IQR) | 14.5 (5.75–24.0) |
| Age at first neutropenia, months, median (IQR) | 8.0 (5.0–12.0) |
| ANC, cells/μL, median (IQR) | 200.0 (100.0–600.0) |
| ANC < 500 cells/μL | 21/29 (72.4%) |
| ANC 500–999 cells/μL | 6/29 (20.7%) |
| ANC 1000–1499 cells/μL | 2/29 (6.9%) |
| Affected relative/family history documented | 12/28 (42.9%) |
| Diagnostic delay among patients with neutropenia preceding diagnosis, months, median (IQR) | 6.0 (3.0–16.0) |

Table 2
Clinical manifestations, diagnosis, management and outcomes of neutropenic XLA patients (n = 29)

| Variable | Value (%) |
|---|---|
| Pneumonia/pleuropneumonia | 10/29 (34.5) |
| Skin/soft tissue infection | 10/29 (34.5) |
| Sepsis or bacteremia | 6/29 (20.7) |
| Fever/neutropenic fever only | 9/29 (31.0) |
| Family-history screening | 2/29 (6.9) |
| Diarrhea/dysentery | 2/29 (6.9) |
| Septic arthritis | 1/29 (3.4) |
| Neutropenia preceding XLA diagnosis | 19/29 (65.5%) |
| Neutropenia coinciding with diagnosis, or preceding IVIG initiation | 10/29 (34.5%) |
| Diagnostic delay among the 19 patients in whom neutropenia clearly preceded diagnosis, months, median (IQR) | 6.0 (3.0–16.0) |
| IVIG | 29/29 (100.0%) |
| G-CSF | 4/29 (13.8%) |
| Chronic lung disease | 1/29 (3.4%) |
| Fatal infection | 1/29 (3.4%) |

Among all 29 patients. By definition, neutropenia was documented before initiation of IVIG in all 29 patients; the two categories distinguish those in whom it preceded the diagnosis of XLA by more than a nominal interval (19) from those in whom it coincided with diagnosis, or preceded diagnosis by only two weeks to two months (10).

Table 3
Microbiological findings (non-mutually exclusive)

| Variable | Value (%) |
|---|---|
| Patients with documented pathogen | 11/29 (37.9) |
| Pseudomonas aeruginosa | 7/29 (24.1) |
| Haemophilus influenzae | 2/29 (6.9) |
| Streptococcus pneumoniae | 2/29 (6.9) |
| Salmonella species | 1/29 (3.4) |
| Adenovirus | 1/29 (3.4) |
| Giardia | 1/29 (3.4) |

# Discussion

In this multicenter cohort of 61 patients with X-linked agammaglobulinemia (XLA), neutropenia was observed in nearly half of patients and frequently represented the earliest documented laboratory abnormality, preceding diagnosis by several months. Neutropenia and neutropenia related infections as an early sign of XLA is the most common presenting finding, suggesting that neutropenia may be significantly more common in XLA than previously appreciated, emphasizing its recognition as an important early manifestation of disease. Beyond its prevalence, neutropenia may contribute to delayed diagnosis, additional investigations, and possibly preventable infectious morbidity, as the diagnostic evaluation often focuses on alternative causes of neutropenia, while assessment of serum immunoglobulin levels may not be routinely performed

The prevalence of neutropenia observed in our cohort (47.5%) was considerably higher than rates reported in previous studies. A summary of comparator XLA cohorts is provided in table S3. Winkelstein et al. [8] reported neutropenia as an initial presenting feature in 11% of a 201-patient US registry cohort, a nationwide Japanese survey found neutropenia in 16/87 patients (18%) with confirmed BTK mutations [9], while case series and literature reviews have cited rates as high as 18–25% [1, 2]. Several factors may account for this discrepancy. First, our study was conducted at tertiary pediatric immunology centers, which may have enriched the cohort for patients with more severe or atypical presentations. Second, differences in timing of neutrophil assessment may influence reported prevalence and inclusion of secondary causes of neutropenia, mainly co-infections. While some studies reported neutropenia only at diagnosis, our analysis included episodes documented prior to or at the time of diagnosis, with exception of three cases that were recognized due to family history without clinical symptoms. In our study neutropenia frequently preceded the diagnosis of XLA, in 65% of the patients with available timing data, neutropenia preceded the diagnosis of XLA. In several of these patients, this led to investigations for isolated neutropenia, infectious etiologies, or primary hematologic disorders before humoral immunodeficiency was considered. Four patients underwent bone marrow examination; marrow

evaluation in this clinical context has previously been reported to reveal a maturation arrest at the promyelocyte/myelocyte stage [10]. Consistent with prior reports describing G-CSF responsiveness of XLA-associated neutropenia [11], four patients in our cohort received G-CSF. Others experienced prolonged intervals between the onset of neutropenia and the diagnosis of XLA. Although diagnostic delay is multifactorial, our findings suggest that severe or unexplained neutropenia in male infants should prompt consideration of an underlying antibody deficiency, particularly when accompanied by recurrent bacterial infections, failure to thrive, or a suggestive family history.

Severe bacterial infections were frequent among neutropenic patients, including a notable frequency of Pseudomonas aeruginosa. Invasive pseudomonal disease in infancy often raises concern for congenital neutropenic syndromes, severe congenital neutropenia, or phagocytic disorders such as chronic granulomatous disease. However, our findings indicate that XLA should also be included in the differential diagnosis in this setting. A Taiwanese XLA cohort (n = 19 with confirmed BTK mutations) reported an even higher rate of Pseudomonas sepsis (74%), which was more common than recurrent sinopulmonary infections in that population and was associated with recurrent hemophagocytic lymphohistiocytosis, both of which were reduced by regular immunoglobulin replacement therapy [12]. Together with our findings, this suggests that susceptibility to Pseudomonas infection may be a more prominent feature of XLA than previously emphasized. Recognition of this association may facilitate earlier immunologic evaluation and reduce unnecessary invasive procedures. Importantly, quantitative serum immunoglobulin testing is inexpensive, widely available, and may rapidly identify patients with underlying humoral immunodeficiency.

The mechanisms underlying neutropenia in XLA remain incompletely understood. BTK is expressed not only in B lymphocytes but also in cells of the myeloid lineage. Fiedler et al. demonstrated impaired granule protein expression and functional maturation in BTK-deficient mice, despite enhanced granulocyte-monocyte progenitor output [13]. In human neutrophils, BTK has been shown to negatively regulate reactive oxygen species production and stimulation-induced apoptosis following Toll-like receptor and TNF-receptor engagement, acting as a direct regulator of neutrophil activation and survival [21], providing evidence for a cell-intrinsic role of BTK within the neutrophil lineage itself, beyond its effects on myeloid progenitor maturation in murine models. Whether this murine mechanism fully accounts for the neutropenia observed clinically in XLA remains uncertain, particularly given its apparent reversibility with immunoglobulin replacement. Neutropenia has also been described in other forms of agammaglobulinemia caused by defects in early B-cell development [14–17], suggesting that profound B-cell deficiency itself may contribute to impaired neutrophil homeostasis. Isolated reports have documented similar findings in other inherited disorders of early B-cell development, including *BLNK* [18] and *TCF3* [19] deficiencies. Together with the shared developmental phenotype observed in other forms of agammaglobulinemia, such as *CD79A* [20] deficiency, these observations raise the possibility that impaired neutrophil homeostasis may represent a broader consequence of disrupted B-cell development [21]. However, the available evidence is limited to individual case reports and small case series, precluding conclusions regarding the prevalence, clinical significance, or underlying mechanisms of neutropenia across these disorders. Nevertheless, these observations, together with our findings,

support considering inherited defects of early B-cell development in the differential diagnosis of otherwise unexplained neutropenia, particularly when accompanied by hypogammaglobulinemia or absent peripheral B cells.

Additional mechanisms have been proposed, including infection-mediated marrow suppression, altered cytokine signaling, immune dysregulation, and impaired interactions between B cells and the innate immune compartment. A microbiologically documented pathogen was identified in only 11/29 patients (37.9%), suggesting that documented bacterial infection alone does not fully explain the occurrence of neutropenia in this cohort.

Although longitudinal neutrophil count data were not systematically collected in this retrospective dataset and could therefore not be analyzed here, prior reports describe resolution of neutropenia following initiation of immunoglobulin replacement therapy in patients with XLA, suggesting that the underlying process may be at least partially reversible rather than reflecting a fixed defect in granulopoiesis. This pattern is consistent with observations in other antibody-deficient populations receiving IVIG, in which acute neutropenic episodes were closely associated with concurrent infection, and immunoglobulin replacement reduced but did not eliminate their occurrence [22],

Our study has several limitations. Its retrospective design precludes definitive conclusions regarding causality, and data were collected over nearly two decades from multiple institutions, introducing the possibility of ascertainment bias and variability in clinical practice. Longitudinal laboratory data were not uniformly available, and genotype–phenotype correlations could not be systematically evaluated. Furthermore, referral to tertiary immunology centers may have resulted in overrepresentation of patients with severe infectious manifestations, potentially inflating the observed prevalence of neutropenia. Although all participating centers contributed data. data were incomplete for some patients, particularly those diagnosed many years earlier or followed before implementation of electronic medical records; consequently, the actual prevalence of neutropenia in this cohort may have been underestimated. Despite these limitations, this study represents one of the largest cohorts specifically examining neutropenia in patients with XLA. Our findings highlight that neutropenia is not merely an occasional laboratory abnormality but may constitute an important presenting feature of disease.

Children with XLA may initially present to hematologists rather than immunologists. In male infants presenting with persistent or severe neutropenia, particularly when accompanied by bacterial infections or Pseudomonas aeruginosa, early measurement of serum immunoglobulins and peripheral B-cell enumeration may substantially shorten the diagnostic pathway and avoid unnecessary invasive investigations. Earlier recognition of XLA may facilitate timely initiation of immunoglobulin replacement therapy, reduce diagnostic delay, and ultimately improve clinical outcomes.

## Conclusion

Neutropenia was an important presenting manifestation of XLA in this multicenter cohort and was typically severe. In most of the patients, neutropenia presented before or at the time of XLA diagnosis.

These findings support routine evaluation for humoral immunodeficiency in male infants and children with persistent or severe neutropenia, particularly when accompanied by bacterial infection.

## Declarations

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# Author Contribution

Author Contributions:NM-study conception and design, patient care, data collection and analysis, manuscript revision; EK - patient care, data collection and analysis, manuscript revision; OT - patient care, data collection and analysis, manuscript writing and revision; RS, SF, AE, SH, AB, AN, DE, SN, DH, AO, ID, AK, OSh, YT, EI, SC, BB, RCC, IL, NS, YP, LA, OSc – patient care, data collection and manuscript revision. AR – statistical analysis and manuscript revision.

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# Data Availability:

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request

Ethics Approval: This study was performed in line with the principles of the Declaration of Helsinki. Local data collection and anonymization were approved by the institutional review board at each participating center in accordance with local regulations. Analysis of the pooled, anonymized dataset was approved by the Institutional Review Board of Shaare Zedek Medical Center (approval SZMC-22-0106).

Consent to Participate: The requirement for informed consent was waived by the local Ethics Committee(s) in view of the retrospective nature of the study and the fact that all procedures performed were part of routine clinical care.

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