Neutrophil Counts—Too Less and Too Many—Both Can Be Immune Deficiency

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Conventionally, neutrophilic leukocytosis in a child with fever is attributed to an infection (most likely a bacterial infection). However, the presence of a low neutrophil count is unusual and must be given due attention. The presence of neutropenia or marked neutrophilia can be marker for underlying primary immune deficiency (PID).

Neutropenia

>1 year	ANC <1,500/mm^3
<1 year	ANC <2,000/mm^3

ANC, absolute neutrophil count

Classification of Congenital Neutropenia

Classification	*Absolute neutrophil count*
Mild neutropenia	1,000–1,500/mm^3
Moderate neutropenia	500–1,000/mm^3
Severe neutropenia	<500/mm^3
Persistent neutropenia	ANC always <1,500/mm^3
Intermittent neutropenia	ANC occasionally <1,500/mm^3
Cyclic neutropenia	ANC with periodic oscillations and nadir <1,000/mm^3

Children presenting with persistent or recurrent neutropenia must be evaluated for underlying PID.

We will discuss a few clinical cases and understand this concept.

Case Descriptions

Case 1

A 4-month-old girl, product of second-degree consanguinity, presented with draining ears from second month of life. She was hospitalized with severe pneumonia.

Family history—first born. No history of sibling deaths.

Investigations:

Complete blood count (CBC):

Hemoglobin (Hb) 8.5 g/dL, total counts (TC) 7,300/mm^3 ($N_9L_{80}M_6E_5$), platelet counts (PC) 523,000/mm^3

Absolute neutrophil counts (ANC): 657/mm^3

Previous records were reviewed

CBC: Hb 9 g/dL, TC 5,200/mm^3 ($N_5L_{75}M_{15}E_5$), PC 236,000/mm^3

ANC: 260/mm^3

CBC: Hb 9.2 g/dL, TC 6,500/mm^3 ($N_7L_{78}M_{12}E_3$), PC 639,000/mm^3

ANC: 455/mm^3

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Neutrophils were persistently reduced. Intermittent monocytosis was noted. Hematologist was consulted and a decision was taken to perform bone marrow examination.

Bone marrow biopsy: Maturation arrest in the myeloid lineage (only precursors in the myeloid lineage were seen). Erythroid and megakaryocytic lineages were normal.

Diagnosis: Severe Congenital Neutropenia

Genetic studies: pathogenic mutation in *ELANE* gene.

Database

Child with recurrent infections

↓

CBC show persistent neutropenia (ANC <1500/mm^3)

↓

Bone marrow examination—arrest in myeloid lineage

↓

Severe congenital neutropenia

↓

Mutation testing (most common: *ELANE* gene)

Clinical Focus

Severe Congenital Neutropenia

Heterogeneous group of disorders characterized by persistent neutropenia.

ANC <1500/mm^3 (and mostly <500).

Severe infections in early childhood (pneumonia, otitis media, mastoiditis).

Bone marrow examination: arrest in myeloid lineage.

Mutations in *ELANE*, *HAX1*, *WAS*, *SBDS*, *SLC37A4*, *G6PC3*, etc.

Treatment: granulocyte—colony stimulating factor (G-CSF) therapy, bone marrow transplant.

Case 2

A 7-year-old girl presented with recurrent episodes of oral ulcers. These ulcers would last for 3–5 days and recur almost monthly. She had been hospitalized twice for pneumonia. Last year, she also had ear discharge.

She had undergone multiple blood tests and when the records were analyzed, the following was noted:

CBC: Hb 10.2 g/dL, TC 5,200/mm^3 ($N_5L_{75}M_{15}E_5$), PC 436,000/mm^3
ANC: 260/mm^3
CBC: Hb 10 g/dL, TC 8,200/mm^3 ($N_{65}L_{25}M_{05}E_5$), PC 239,000/mm^3
ANC: 5,330/mm^3
CBC: Hb 9.2 g/dL, TC 6,500/mm^3 ($N_7L_{78}M_{12}E_3$), PC 539,000/mm^3
ANC: 455/mm^3
CBC: Hb 9 g/dL, TC 7,500/mm^3 ($N_{78}L_{12}M_7E_3$), PC 639,000/mm^3
ANC: 5,850/mm^3

This child had intermittent neutropenia (and monocytosis too).

She was suspected to have cyclic neutropenia and serial CBC was asked for. In order to diagnose cyclic neutropenia, the CBC must be performed twice a week for 6 weeks.

Date	*Hb*	*TC*	*DC*	*PC*	*ANC*
1st June	10	7,600	$N_{60}L_{30}M_6E_4$	450,000	4,560
4th June	10.2	6,500	$N_{45}L_{40}M_8E_7$	300,000	2,925
7th June	**9.5**	**4,000**	$\mathbf{N_5L_{65}M_{25}E_5}$	**230,000**	**200**
10th June	**9.8**	**4,200**	$\mathbf{N_{10}L_{60}M_{20}E_7B_3}$	**200,000**	**420**
13th June	10	6,700	$N_{45}L_{50}M_3E_2$	223,000	3,015
16th June	10.3	7,000	$N_{67}L_{25}M_6E_2$	350,000	4,690
19th June	10.5	8,700	$N_{70}L_{22}M_5E_3$	340,000	6,090
22nd June	10	7,700	$N_{58}L_{25}M_9E_6B_2$	245,000	4,466
25th June	10.2	8,340	$N_{35}L_{55}M_5E_5$	234,000	2,905
28th June	**9.4**	**4,100**	$\mathbf{N_3L_{60}M_{27}E_7B_3}$	**165,000**	**123**
1st July	**10.3**	**4,500**	$\mathbf{N_{10}L_{62}M_{20}E_6B_2}$	**187,000**	**450**
4th July	10.2	8,000	$N_{68}L_{24}M_6E_2$	289,000	5,440

Bold values in the table indicate the periods of neutropenia. Note that ANC dropped to less than 1,000 on two occasions (3 weeks' apart)

Diagnosis: Cyclic Neutropenia

Genetic testing: pathogenic mutation in ELANE gene

Clinical Focus

Cyclic Neutropenia

Neutropenia occurs once in 21–25 days.

Neutropenia lasts for 3–5 days.

During periods of neutropenia, children develop oral mucositis and infections (otitis media, pneumonia, etc.).

Bone marrow examination done at the time of neutropenia: arrest in myeloid lineage.

Mutations in *ELANE* gene.

Treatment: G-CSF therapy.

Case 3

A 3-year-old boy presented with fourth episode of pneumonia. He was hospitalized for 7–10 days during each of these episodes, treated with antimicrobials, and received oxygen therapy. In between these episodes, he was well.

He had been investigated extensively:

- Echocardiography: normal
- Computed tomography (CT) chest: no anomaly
- Sweat chloride test: normal
- Nuclear scan for gastroesophageal reflux (GER): normal
- HIV rapid test: nonreactive

He was referred to pediatric immunology services.

Investigations:

CBC: Hb 9.5 g/dL, TC 6,300/mm^3 ($N_9L_{80}M_6E_5$), PC 320,000/mm^3
ANC 567
Immunoglobulins (IgS)
IgG <130 mg/dL (345–1,236)
IgA <30 mg/dL (14–159)
IgM <20 mg/dL (43–207)

All the IgS were Low

Next step: B-cell counts were performed.

B cells (CD19): 0.5% (*n* 10–15%).

B Cells were Absent

Genetic testing—mutation in *BTK* gene.

Diagnosis—X-linked agammaglobulinemia (XLA).

Database

3-year-old boy with recurrent pneumonia
↓
Neutropenia
↓
Low IgS and absent B cells
↓
Diagnosis: XLA

Clinical Focus

X-linked Agammaglobulinemia

(Previously called Bruton's agammaglobulinemia)

Boys are affected.

Recurrent pneumonia, otitis media, skin infections, and diarrhea.

Absent tonsils and nonpalpable lymph nodes.

Low immunoglobulins (low IgS) and absent B cells.

Mutation in the BTK gene.

Note: in the presence of an infection, patients with XLA can develop neutropenia.

Do Very High Neutrophil Counts Point toward a PID?

Have you seen children with total white blood cell counts of >100,000/mm^3?

I am sure you would have thought of leukemia or a leukemoid reaction in these cases. But most often these children would have a marked lymphocytosis and the diagnosis in those cases would be acute lymphoblastic leukemia.

But have you seen a child with WBC counts >100,000/mm^3 and neutrophilic predominance?

Let me discuss a case.

Case 4

A 9-month-old girl presented with chronic diarrhea for the past 3 months. She had developed perianal ulcers. She had been hospitalized at multiple places and investigated. As she had persistent leukocytosis, she was thought to have sepsis and given a variety of antibiotics but with no relief.

She was referred to our department with a suspicion of PID. Her previous records were analyzed.

CBC: Hb 10.2 g/dL, TC 92,000/mm^3 ($N_{85}L_{10}M_4E_1$), PC 536,000/mm^3
ANC: 78,200/mm^3
CBC: Hb 10 g/dL, TC 108,200/mm^3 ($N_{82}L_{12}M_5E_1$), PC 139,000/mm^3
ANC: 88,560/mm^3
CBC: Hb 9.2 g/dL, TC 86,500/mm^3 ($N_{87}L_8M_3E_2$), PC 465,000/mm^3
ANC: 75,255/mm^3
CBC: Hb 9 g/dL, TC 67,500/mm^3 ($N_{82}L_{10}M_7E_1$), PC 639,000/mm^3
ANC: 55,350/mm^3

This child had persistent neutrophilic leukocytosis and the counts remained high even when the child was clinically well. Is this the pattern that you note in sepsis? The answer is NO.

Persistent severe neutrophilia in a child with recurrent infections → think of leukocyte adhesion deficiency (LAD)

Further investigations

CD18 expression on neutrophils was studied by flow cytometry.

CD18 0.1% (normal—99%)

Diagnosis: LAD type I

Database

Child with recurrent infections/nonhealing ulcers
↓
CBC shows persistently high neutrophil count (ANC >20,000/mm^3)
↓
Leukocyte adhesion deficiency
↓
CD18 expression reduced on neutrophils (flow cytometry)

Clinical Focus

Leukocyte Adhesion Deficiency

Group of genetic disorders characterized by defect in adhesion of neutrophils to the endothelium of blood vessels.

Autosomal recessive inheritance.

Clinical features—delay in the fall of umbilical cord, omphalitis, perianal ulcers, recurrent pneumonia, and diarrhea.

No pus formation.

CBC: very high neutrophil count;

White cell counts may be as high as 100,000/mm^3.

LAD I—absent CD18 expression on neutrophils, mutation in *ITGB2* gene.

LAD II—absent CD15a expression on neutrophils, Mumbai blood group, mutation

in GDP-fucose transporter gene

LAD III—defect in integrin activation, mutation in *FERMT3* gene

Message

- When children present with recurrent infections and/or mucositis, one must carefully look at the neutrophil counts. Presence of intermittent or persistent neutropenia may point toward an underlying immune deficiency.
- Intermittent neutropenia may be noted in children with XLA and hyper-IgM syndrome.
- Children with persistent neutrophilic leukocytosis must be investigated for LAD.