
بسم الله الرحمن الرحيم

Autoimmune neutropenia of infancy and childhood

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Causes of Neutropenia

- Acquired
  - Infection
  - Infiltrative bone marrow disease
  - Immune mediated
  - Medication
- Congenital
  - Severe Congenital
  - Cyclic neutropenia
  - Chronic benign neutropenia of childhood
  - Chronic neutropenia of childhood
  - Benign Ethnic Neutropenia
  - Schwachman Diamond syndrome

Intrinsic defects in Myeloid cells or their progenitor

- Reticular Dysgenesis
- Severe congenital neutropenia(Kostmann's Dis.)
- Cyclic Neutropenia
- Myelokathexis
- Schwachman's Syndrome
- Dyskeratosis Congenita
- Familial benign neutropenia
- Bone marrow failure syndromes

Neutropenia caused by Extrinsic Factors

- Infection
- Drug induced
- Autoimmune neutropenia
- Immune neonatal neutropenia
- Neutropenia associated with immune dysfunction
- Neutropenia associated with metabolic diseases
- Nutritional deficiencies
- Reticuloendothelial sequestration
- Bone marrow infiltration
- Chronic idiopathic neutropenia

Case report

- An 8-month-old male infant presented at the emergency room with a 5-days history of fever up to 39.7 °C, cough and runny nose
- Physical exam normal
- WBC : 6500 poly : 2% Monocyte : 10% Lymph : 85% Hb : 12 g/dl Plt : 450000
- Influenza A positive
- He received supportive care and improved after 3days and discharged
- Neutropenia continued for one year without treatment and has improved spontaneously after that

Immune Neutropenia of Infancy/Childhood

- the median age at diagnosis is 7–9 months
- incidence is 1 out of 100,000 children under 10 years of age
- Most patients recover by 4–5 years of age and in about 90% resolution occurs before 2 years of duration
- Serious Infections occur only in about 12–20% of affected children
- A mild associated leukopenia is possible and about a quarter of children present monocytosis
- no clear sex difference in incidence rate between males and females

Human neutrophil antigens (HNAs)

Glycoprotein	Antigen	Old nomenclature
FcγRIIIb (CD16b)	HNA-1a	NA1
	HNA-1b	NA2
	HNA-1c	NA3-SH
	HNA-1d	
Gp 58–64 (CD177)	HNA-2a	NB1
Choline transporter-like protein 2	HNA-3a	5b
	HNA-3b	5ba
CD11b	HNA-4a	MART
	HNA-4bw	
CD11a	HNA-5a	OND
	HNA-5bw	

HNA-1a and HNA-1b frequency.

HNA-1a and HNA-1b frequency

	HNA-1a	HNA-1b
Western Japan	-	99.5%
Asian Indians	30%	70%
Black (USA)	31%	69%
White (USA)	37%	63%
Turkey	42%	56%
Italy	49%	84%
Tunisian	52%	86%
Hispanic (USA)	53%	47%
Native Americans (USA)	55%	45%
Brazil	65%	83%
Chinese	91%	54%

Diagnosis

- The granulocyte-specific antibodies causing neutropenia are directed against the cell surface membrane and have no relationship with antineutrophil cytoplasmic antibodies (ANCAs) in the vast majority of cases
- Direct test: false positive
- Indirect test : false negative
- To reduce the false negative rate of indirect testing, the neutrophil panel should include at least one homozygous HNA-1a/1a and one HNA-1b/1b test cell, since the difficulty of autoantibodies binding to granulocytes coming from HNA-1a/1b heterozygous donors is well known

Diagnosis

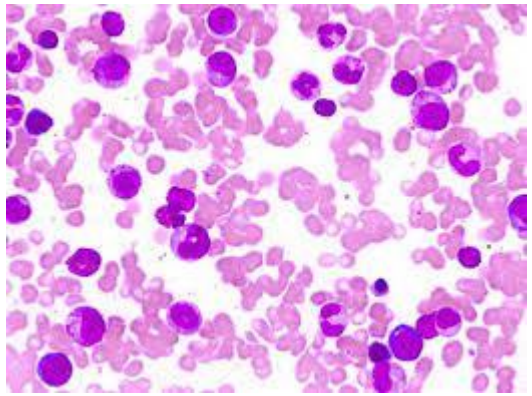
- reports from the International Granulocyte Immunology Workshop suggest the use of a combination of the granulocyte immunofluorescence test (GIFT) and the more time-consuming granulocyte agglutination test (GAT)
- Thanks to a fluorescein isothiocyanate (FITC) conjugated antibody, in GIFT it is possible to identify antibodies bound to the neutrophil surface either by flow cytometry or by fluorescence microscopy
- microscope detection is more time-consuming, requires a lot of expertise, and consequently has high interobserver variability. Flow cytometry overcomes these pitfalls but still has some drawbacks:

1. Sometimes interpretation is made difficult by high background reactivity.

2. Sometimes the assessment of antibody specificities is limited by the presence of immune complexes or anti human leukocyte antigen (anti-HLA) antibodies that may also bind to granulocytes.

Bone marrow aspiration

- bone marrow is not informative usually is normal
- hyper cellular marrow generally with a late maturational arrest may support the diagnosis.
- postpone the procedure until after at least the result of the first autoantibody assay if the child's age is typical, if there is no other associated cytopenia, if there are no severe infections in the medical record, and if there are no clinical or laboratory criteria for suspicion of leukemia



differential diagnosis of AIN

- Infection-induced neutropenia
- Pregnancy or delivery-related neutropenias.
- Alloimmune neonatal neutropenia (ANN)
- Neonatal alloimmune neutropenia secondary to maternal autoimmune neutropenia
- Severe congenital neutropenias (SCN)
- Autoimmune neutropenia associated with other autoimmune diseases (often called secondary autoimmune neutropenia)
- Neutropenia associated with immunodeficiency(hyperigM syn,Good syn,CVID
- Neutropenia secondary to drug administration
- Autoimmune neutropenia associated with neoplasm
- More rarely neutropenia can be related to vitamin B12, folate or copper deficiency

AIN work-up

Investigation	Time
Immunoglobulin dosage and lymphocyte subpopulations study	At diagnosis. Consider repeating in case of persistence of neutropenia 3 years since the diagnosis or after 5 years of age.
Full blood count	Every 1–3 months.
Bone marrow aspiration	In the presence of clinical signs suggesting a diagnosis re-evaluation.
Enlarged panel of autoimmunity	In case of persistence of neutropenia 3 years since the diagnosis or after 5 years of age.

Management

- Severe infectious complications are overall less frequent in AIN than in genetic neutropenias
- With fever early use of antibiotics such as amoxicillin ± clavulanate
- If an underlying immunodeficiency is ruled out, vaccinations with live vaccines can be performed
- cotrimoxasol prophylaxis ?
- G-CSF 1-2 microgram
- intravenous immunoglobulin, steroids, cyclosporine or anti-CD20 do not have a role in childhood.

conclusion

- Autoimmune neutropenia of infancy (AIN), also called primary autoimmune neutropenia, is a disease in which antibodies recognize membrane antigens of neutrophils, mostly located on immunoglobulin G (IgG) Fc receptor type 3b (FcγIIIb receptor), causing their peripheral destruction.
- It is the most frequent type of neutropenia in children under 3–4 years of age
- in most cases shows a benign, self-limited course.
- The diagnosis is based on evidence of indirect antineutrophil antibodies, whose detection frequently remains difficult