Immune neutropenias of infancy and childhood

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Background: Anti-neutrophil antibodies are a well-recognized cause of neutropenia, producing a potential increase in risk of infection: in the majority of patients antibodies react against antigens located on the IgG Fc receptor type 3b (FcRIIIb), but other target antigens have been identified.

Data sources: In this review the most important papers of auto and alloimmune neutropenias of infancy and childhood were analyzed. PubMed, Google Scholar and Thompson ISI Web of Knowledge were searched for identifying relevant papers.

Results: Primary autoimmune neutropenia of infancy is mostly a benign condition with self-limited course, whereas isolated alloimmune neonatal neutropenia or secondary autoimmune neutropenia may be occasionally complicated by severe infections.

Conclusion: Granulocyte colony stimulating factor is an effective therapy for patients affected by all types of autoimmune and alloimmune neutropenia, even though most of them do not need any therapy.

Key words: immune;
infancy;
neutropenia

Introduction

In Caucasian newborns and toddlers from two weeks up to 1 year of life, the lower limit of absolute neutrophil count (ANC) is $1.0×10^9$/L, whereas it is $1.5×10^9$/L from >1 year to adulthood.[1] In newborns of 6-24 hours of life, neutropenia is defined as less than 6.0-$7.0×10^9$/L, after that there is a slow decrease and the limit (the 5th percentile) is less than $3.0×10^9$/L at about 72 hours of age.[2] In preterms of 28-36 weeks of gestational age (GA), the 5th percentile is about $3.0×10^9$/L at 24 hours of age and about $1.0×10^9$/L at 72 hours of life;[2] in extreme preterms (GA <28 weeks), the 5th percentile is at about $1.0×10^9$/L immediately after birth.[2] Moreover, there are many factors, other than GA, that may interfere with the cutoff. For example:

- Sex: female neonates have neutrophils averaging $2.0×10^9$/L higher than males.[2]
- Type of delivery: comparing cesarean section deliveries with labor to cesarean section deliveries without labor, newborns whose mothers labored present higher ANC.[2]
- Intrauterine growth retardation: comparing small for gestational age to appropriate for gestational age newborns, the second group shows higher ANC.[3]

Neutropenia is a common hematological finding that, in Caucasian children older than 1 year of age, is defined as severe (neutrophils <$0.5×10^9$/L), moderate (between 0.5 and $1.0×10^9$/L) and mild (between 1.0 and $1.5×10^9$/L).[1] Other populations, such as American Blacks, Blacks of South African extraction and Mexican-Americans,[4-6] can present lower normal inferior limits of ANC.

Sometimes neutropenia is linked to the production of antibodies against antigens of neutrophil surface. Table 1 shows human neutrophil antigens (HNA).

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Table 1. Human neutrophil antigens (HNA)

Glycoprotein	Antigen	Old nomenclature
FcRIIIb (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	

CD: cluster of differentiation.

HNA-1, the glycoprotein FcRIIIb, has some isoforms that are the most involved both in autoimmune neutropenia (AIN) and alloimmune neutropenia (AN). There is a new entry, the HNA-1d, recently identified in two newborns.[7] The antigens vary in frequency among different ethnic populations.[8-13]

It is important to immediately highlight that granulocyte-specific antibodies causing AIN or AN, are not related to anti-neutrophil cytoplasmic antibodies (ANCA), and often there are difficulties in their dosage; in fact the direct granulocyte test (recognizing antibodies fixed on the patient's neutrophil surface) presents an elevated number of false positives[14,15] and the indirect test (recognizing granulocyte-specific antibodies in the serum of the patient) suffers from a high false negative rate.[16] And so, since the diagnosis of all types of immune neutropenias can be confirmed only when the indirect test is positive, it would be better to use an association of two techniques, i.e. immunofluorescence and agglutination, to increase the accuracy of diagnosis.[17] If the first determination is negative, a repetition should be considered.[18] Furthermore, monoclonal immobilization of granulocyte antigen, a cumbersome technique whose use is restricted only to certain laboratories, can be used as confirmatory test.[17,19]

Concerning the therapeutic aspects the granulocyte-colony stimulating factor (G-CSF or GCSF), a protein that stimulates the bone marrow to produce neutrophil, has become the standard of treatment in all types of autoimmune and alloimmune neutropenias, since it is ineffective only in a small minority of patients.

Tables 2 and 3 report two possible classifications of AIN and AN. In this review, I will only discuss the most typical immune neutropenias of childhood (primary/isolated autoimmune neutropenia of infancy/childhood, alloimmune neonatal neutropenia, alloimmune neonatal

Table 2. Classification of autoimmune neutropenias

Autoimmune neutropenia of infancy/childhood (primary/isolated)
Autoimmune neutropenia of adulthood (primary/isolated)
Secondary/associated autoimmune neutropenia
Autoimmune neutropenia after bone marrow transplantation

Table 3. Classification of alloimmune neutropenias

Alloimmune neonatal neutropenia
Alloimmune neonatal neutropenia secondary to autoimmune maternal neutropenia
Transfusion-related acute lung injury
Transfusion-related alloimmune neutropenia
Febrile transfusion reactions
Alloimmune neutropenia after bone marrow transplantation

neutropenia secondary to autoimmune maternal neutropenia, and secondary/associated autoimmune neutropenia) and not some others, such as immune neutropenias after bone marrow transplantation or transfusion related acute lung injury (TRALI), whose interest is exclusively restricted to pediatric hemato-oncologists or transfusionists.

Autoimmune neutropenia of infancy or childhood

In the literature both "infancy" and "childhood" are used but I think infancy is more appropriate since the vast majority of patients present under 18 months of age. It has been reported that the incidence is one out of 100 000 children of less than 10 years of age,[20] but this is probably an underestimation. In contrast to isolated adulthood AIN, more frequent in females,[21] there is no sex difference in incidence. The median age at diagnosis is 7-9 months,[16,20,22] and infancy AIN is exceptional at less than 1 month of age.[16,23,24] In about 90% of the patients remittance occurs after less than 2 years.[16] There is a theoretical but obvious relationship between spontaneous recovery and pathogenesis, which is still unclear. Is there a modification of antigens after drug use, or molecular mimicry of microbial antigens and post-infection autoantibodies? Another hypothesis is that the suppressor system in these patients is immature and that the spontaneous recovery corresponds with the complete development of a suppressor T-cell counterpart. Even though more than two-thirds of patients have less than 0.5×10^9/L neutrophils, severe infections present only in about 12%-20% of them[16,25] and the vast majority show an infection rate not different from that of the median of peers; in about 8%-27% of cases the diagnosis is fortuitous.[16,26]

Frequently mild leukopenia is associated and about 25% of children present monocytosis,[16,27] which, together with the prompt neutrophil increase in the case of infection, probably contribute to benign disease. In most cases, bone marrow (BM) presents a reduced number of metamyelocytes, bands, or mature neutrophils,[16] but is not really informative, as is cytofluorimetry, frequently showing only an increase of CD34+ stem cells:[28] the existence of autoantibodies harnessing granulocyte precursors can explain the occasional evidence of myeloid hypoplasia.[29,30]

IgG is the most frequently involved immunoglobulin class (85%) and complement can be activated or not.[16] There is also some evidence that different genotypes can play a role in predisposing infancy AIN:
- There is an increase in HNA-1a allelic frequency, not only in Japanese and

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Taiwanese populations but also in Western populations.[26,31,32]

- There is also a significant association with HLA DR2[33] and with HLA DQB1*0503.[31]

Due to the high false negative rate of indirect testing some patients could not be classified as affected by AIN and, consequently, defined as suffering from "idiopathic neutropenia".

G-CSF, at an initial dose of 1-2 μg/kg, is the therapy of choice in case of severe infections: the dosage can be increased with the goal of achieving an ANC of at least $1.0×10^9$/L. In some papers trimethoprim/sulfamethoxazole was efficient in diminishing the infectious rate,[34] but the course of disease is extremely mild in the vast majority of patients and so I think that antibiotic prophylaxis should be avoided.[35]

Neonatal alloimmune neutropenia

For the development of neonatal alloimmune neutropenia (NAN), there should be a fetomaternal granulocyte mismatch and the pregnant woman should be alloimmunized against the granulocyte antigens; the indirect anti-neutrophil antibodies are contemporarily positive in the newborn and the mother, and the diagnosis is certain if there is a positive cross-match between maternal sera and paternal granulocytes. There are, in a manner of speaking, three levels of incidence:

- First level: fetomaternal incompatibility. Prospective data on more than 1000 Polish pregnant women indicate that it occurs in about 20% of pregnancies.[36]
- Second level: alloimmunization. According to studies on unselected healthy pregnant women the incidence of alloimmunization is 0.6-1.1%.[36-38]
- Third level: NAN. The incidence is classically reported to be 1-2 out 1000 newborns, but in a group of more than 24 000 neonates Zupanska diagnosed only 4 patients.[36] So it seems that the frequency can be expected to be roughly one per 6000 newborns.

Serious infections, above all of skin and umbilical cord, are present in 1 out of 5 patients.[37,39-40] The duration of neutropenia is on average 1-4 months.[37-39] There are not many reports on therapy[39,40] and an initial dose of 1-2 μg/kg of G-CSF can be attempted even though some reports suggest starting with a dosage of 10 μg/kg of G-CSF.[40] There is no agreement about the duration, but, considering that neutropenia lasts only a few weeks and that there are some reports of serious complications of infection, an administration up to recovery of an ANC higher than $1.0×10^9$/L should

probably be considered. Finally there are few cases of total inefficacy of G-CSF[41-43] and in some of them *i.v.* immunoglobulins at 0.8-1 g/kg were effective.[41]

Neonatal alloimmune neutropenia secondary to maternal autoimmune neutropenia

This is the rarest immune neutropenia of early infancy. Obviously, the duration of this neutropenia is on average the same as "classic" NAN. There are less than 10 patients reported[44-47] and, among them there are 2 pairs of brothers:[44, 45] in the first pregnancy both mothers and neonates were not treated with G-CSF and both infants suffered from severe infections. On the occasion of the second pregnancies both mothers were given low-dose G-CSF and both newborns didn't have neutropenia. So it seems that G-CSF must be given to the mothers. The experience in dealing with pregnant women affected by severe congenital neutropenia prove that G-CSF administration in pregnancy is safe.

Secondary/associated autoimmune neutropenia

Secondary/associated AIN is more typical of adulthood or late childhood, but there are some cases, the vast majority presenting along with autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP), where the onset may be very precocious.

AIN associated with other autoimmune diseases

In a fundamental paper, Bruin et al[48] reported the principal differences between primary and secondary autoimmune neutropenias:

- Age of appearance: later in the secondary type (<1 year *vs.* 0.5-15 years).
- Spontaneous remittance: exceptional in secondary autoimmune neutropenias (all but one associated with other autoimmune diseases) *vs.* in almost all cases of primary type (all infancy AIN).
- Infectious burden: higher in secondary type.

The most frequently associated diseases in childhood

Table 4. Autoimmune diseases associated to autoimmune neutropenias

Systemic lupus erythematosus

Sjogren's syndrome

Primary biliary cirrhosis

Autoimmune lymphoproliferative syndrome

Rheumatoid arthritis and Felty syndrome

Autoimmune thyroiditis

Crohn's disease

Autoimmune hepatitis

are AIHA and ITP, but other autoimmune disorders, such as systemic lupus erythematosus, Sjogren's syndrome or autoimmune lymphoproliferative syndrome, can be complicated by neutropenia (Table 4).

AIN associated with immunodeficiency

In most cases, neutropenia is not autoimmune, even though there are some immunodeficiencies, such as HyperIgM syndrome[49] and Good syndrome[50] (association of hypogammaglobulinemia with thymoma and autoimmune cytopenias), where an autoimmune mechanism is common. AIN is possible also in common variable immunodeficiency.[51] Similarly to neutropenia associated with other autoimmune diseases and in contrast to the other types of secondary AIN (see below), there is no tendency for spontaneous recovery.

AIN associated with infections

The most important mechanism causing infection related neutropenia is a transient suppression of BM production of neutrophils; only in a small minority it is an autoimmune reaction proven and there are reported associations with human immunodeficiency virus, hepatitis C virus, hepatitis B virus, parvovirus B19, influenza B virus, *Helicobacter pylori* and Epstein Barr virus.[52-57] In the vast majority of cases this neutropenia lasts less than 3 months.[57]

AIN secondary to drug administration

Drugs are the most common cause of an "idiopathic" neutropenia but only a few cases[58] are autoimmune (the major working hypothesis being the hapten hypothesis), since a damage against the myeloid colonies in the bone marrow is probably the most frequent cause. Table 5 reports on which classical criteria basis an agranulocytosis (neutrophils $<0.5\times10^9$/L) can be classified as drug induced (DIA). According to these criteria both late onset neutropenia (for example months after rituximab) and drug induced neutropenia with neutrophils between 0.5×10^9/L and 1.5×10^9/L are

Table 5. Definition of drug induced agranulocytosis

Criteria of drug imputability:
Onset during treatment or within 7 days of previous intake AND
Complete recovery within 1 month of discontinuation
+/- recurrence upon re-exposure to an offending drug
Criteria of exclusion:
History of severe congenital neutropenia or AIN
Existence of underlying hematological disease
Recent infection
Recent Chemo/Radio/Immunotherapy

AIN: autoimmune neutropenia.

not included. There is a high variability (2 days to 2 months) in the duration of drug administration before the appearance of neutropenia.[59] Another important point is age: only about 10% of cases are children and young adults, and the vast majority of these episodes are reported in people over 60 years of age;[60] the phenomenon is probably related to higher medication use among old people. Finally there are at least three known paths through which individual genetics influences the appearance of drug induced neutropenia.

- Drugs and their metabolism. Some single nucleotide polymorphisms in genes controlling drug metabolism can lead to different blood and tissue levels of the medication or its metabolites. For example, a higher proportion of slow acetylators has been shown in patients developing sulfasalazine induced agranulocytosis.[61]
- Association with specific HLA genotypes. For example, an association between HLA-B38 and DR4 has been described in Ashkenazi Jews or DR2-DQ1 in non-Jews suffering from clozapine-related agranulocytosis.[62]
- Disease-drug interaction. Little is known about this phenomenon but it is a fact that, for example, dapsone induced neutropenia is rare when treating leprosy or dermatitis herpetiformis but frequent during malaria prophylaxis, or deferiprone induced agranulocytosis is more common when treating iron overload in Diamond-Blackfan Anemia compared to thalassemia.[63-65]

Hypoplastic bone marrow is found in 2 out of 3 patients.[59] There is a strong tendency of decreasing DIA-associated mortality over time, but this is not definitely related to the G-CSF administration, since improved supportive therapy has probably been decisive in increasing survival too.[59,63]

Until 5 years ago, there were 125 drugs definitely or probably related to agranulocytosis.[59] Methimazole is the most involved drug, and anti-epileptic agents are the most involved class of medications: leukopenia develops in 31.4% of children treated with carbamazepine[66] and in 24% of patients treated with valproate.[67]

AIN secondary to neoplasm

There are not many data and most knowledge is related to thymic neoplasms (about 15 reports)[68] and Hodgkin lymphoma (5 reports),[69] but association with non-Hodgkin lymphoma,[70] Castleman disease,[71] large granular lymphocytosis[72] and melanoma[73] has been published. Regarding the relationship with Hodgkin lymphoma, a neoplasm relatively frequent in childhood,

it must be emphasized that autoimmune cytopenia (typically paraneoplastic phenomena) can present prior to, concurrent with, and at the time of recurrence of neoplasm, and they respond better to chemotherapy than to steroids.

Conclusions

Immune neutropenias are diseases where antibodies recognizing membrane antigens of neutrophils, mostly located on FcRIIIb, cause their peripheral destruction. The isolated AIN of infancy is the most frequent type in children less than 3-4 years of age and shows mostly a benign, self-limited course, whereas an autoimmune neutropenia presenting in older children, if not dependent on drug exposure or infections, is frequently associated with other autoimmune manifestations and has no tendency for spontaneous recovery. The diagnosis is based on evidence of indirect anti-neutrophil antibodies, whose detection frequently remains difficult, and the universally accepted first-line treatment is, currently, G-CSF.

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