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Etiology, clinical outcome, and laboratory features in children with neutropenia: Analysis of 104 cases

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Abstract

Background: Neutropenia is not uncommon in childhood. The aim of our study was to analyze the underlying causes of neutropenia and to evaluate its clinical significance in a series of children referred to our center.
Methods: One hundred and four consecutive children with neutropenia were enrolled in this study. Clinical and laboratory features were analyzed.
Results: The majority of patients (63.5%) showed chronic neutropenia. Among all chronic forms, the most frequent was chronic idiopathic neutropenia (CIN), followed by autoimmune neutropenia (AIN). Congenital neutropenia was identified in 6 patients. Acute neutropenia was mainly due to infections. Overall, at the time of first detection, neutropenia was more frequently severe or moderate. One-third of our patients who presented with severe neutropenia were ultimately diagnosed with a post-infectious acute form. Conversely, nearly half patients with CIN, AIN, or congenital neutropenia showed moderate/mild neutropenia at onset. Among patients with AIN and CIN, nearly half recovered between 7 months and 46 months and approximately one-fourth experienced infectious episodes during follow-up. No significant difference was noticed in terms of mean ANC between patients with and without remission, neither between patients with and without infections.
Conclusions: Our study confirms the great etiological heterogeneity of neutropenia in children. We could not demonstrate a correlation between ANC level at onset and the underlying disorder, nor a correlation between mean ANC and duration of neutropenia or infectious episodes during follow-up. Neutropenia remains a disease of concern to pediatricians, requiring several laboratory investigations, prolonged follow-up, and, in few cases, advanced molecular methods.

Neutropenia, defined by an absolute neutrophil count (ANC) $<1 \times 10^9$/l in infants and $<1.5 \times 10^9$/l thereafter, is not uncommon in pediatric patients (1). Among black populations, lower cutoff values must be considered, because their circulating neutrophils are physiologically reduced (2, 3). Neutropenia can be defined as acute or chronic depending on its duration, lower or higher than 3 or 6 months according to different authors (4–8). The severity of neutropenia depends on the ANC: For patients older than 1 yr of age, neutropenia is defined mild with an ANC between 1 and 1.5×10^9/l, moderate with an ANC between 0.5 and 1×10^9/l, and severe when ANC is below 0.5×10^9/l (1). It is widely accepted that

infective diathesis, in terms of frequency and severity of infections, is proportional to the degree of neutropenia (1, 9). Nevertheless, a lot of children with moderate–severe isolated neutropenia have a benign course (4, 6, 7, 10–14), meaning that other factors may influence susceptibility to infection, such as the speed of onset and the duration of neutropenia, the bone marrow myeloid reserves, the absolute circulating monocyte count, and the functional status of phagocytes (1, 9, 15).

A reduction in circulating neutrophils is caused by several inherited and acquired conditions (16). Noteworthy a large number of neutropenia remains of unknown origin, defined as 'idiopathic'. The differential diagnosis of neutropenia some-

times requires much time and a lot of investigations. Moreover, even when the cause of neutropenia is identified, clinicians have to handle other problems, such as treatment and follow-up schedule. Those aspects still remain controversial and strongly influenced by the single patient's characteristics as well as the clinician's personal experience. In 1994, the International Registry of Severe Chronic Neutropenia (SCNIR) was born to watch over severe chronic forms (17).

This study was undertaken to analyze the underlying causes and the clinical significance of neutropenia in a series of children referred to the Unit of Immunology and Infectious Disease and Unit of Hematology of a large pediatric hospital. To our knowledge, there are few studies examining globally these features in children with neutropenia; the majority of papers focus on fewer issues or specific etiologic categories (4, 6, 7, 11, 18–22).

Methods

Our population is composed by 104 patients, referred to the Unit of Immunology and Infectious Disease and Unit of Hematology of a large pediatric hospital to investigate about a recently detected neutropenia. Chemotherapy-induced neutropenia and those secondary to lympho-myeloproliferative disorders and myelodysplastic syndromes were excluded. The study is a retrospective non-structured analysis of outpatient and inpatient charts of children diagnosed with neutropenia from 2007 to 2010, excluding patients without sufficient diagnostic or follow-up (n = 16). Overall, 53% of children were diagnosed during hospitalization in our pediatric hospital, while the others were referred as outpatients.

We performed a multistep diagnostic workup, on the basis of the recommendations of Italian Association of Pediatric Hematology and Oncology (Associazione Italiana Emato-Oncologia Pediatrica, AIEOP) for diagnosis and follow-up of neutropenia in children, which have been recently published by Fioredda et al. (16). Data collection included as follows:

1 Family history, ethnic origin, occurrence of other neutropenia cases, consanguinity.
2 Personal history focused on occurrence of viral and bacterial infections (onset, number, type, site, frequency and severity and cyclic pattern of infections) as well as on drug assumption (type, duration, dose), particularly those indicated as to be associated with neutropenia.
3 Clinical examination, including anthropometry, performed at entry and during follow-up. In particular, clinical findings suggestive for congenital neutropenia were carefully searched for (dysmorphic features, psychomotor development, skeletal abnormalities, albinism, warts, hearth function, liver and spleen size, presence of enlarged lymph nodes, neurological symptoms).
4 Laboratory examinations: ANC monitoring and first-level investigations, including liver and renal function, serum electrolytes, C-reactive protein, fasting glucose, immunoglobulins level, antineutrophil antibodies with indirect granulocyte immunofluorescence test (GIFT), antinuclear antibodies, serology and/or DNA/RNA analysis of some viral pathogens (CMV, EBV, HHV6, parvovirus B19, HIV) and hemogasanalysis.

5 Bone marrow evaluation (morphologic, virologic analysis, cytogenetic, and immunophenotype) was performed in case of confirmed neutropenia with non-informative first-level investigations and no signs or symptoms specific for an associated disease.
6 If the patients showed signs and symptoms and/or biochemical signs suggestive for an associated disease, advanced-level investigations were performed according to possible etiology (16). For example in case of suspected immunodeficiency, standard peripheral blood flow cytometry analysis (CD3 +, CD4 +, CD8 +, CD19 +, CD16 + 56 +) was performed, as well as IgG subclasses and evaluation of specific antibody responses toward vaccination; when indicated, we also performed CD40 ligand expression, determination of naïve CD45RA and memory subsets on CD4 + and CD8 + T cells, peripheral B-cell subpopulation phenotyping, and molecular analysis. Advanced metabolic examination included urinary organic acids, urinary and serum amino acids, and other supplementary investigations addressed by clinical consultants of metabolic disease, to exclude the metabolic diseases usually associated with neutropenia (glycogenosis Ib, organic acidosis, tyrosinemia, Barth syndrome, Gaucher disease and aminoacidopathies). The following microbiology investigations were performed on body fluid cultures, according to clinical indications: blood culture and/or rapid molecular PCR assays for bacterial and fungal DNA, urine culture, pharyngeal bacterial swab. When marrow morphology showed maturation arrest at the stage of pro-myelocyte/myelocyte and/or the presence of a cytogenetic clone or significantly reduced cellularity, ELANE and HAX-1 mutations were tested. Other molecular analysis depended on clinical or laboratory features specific for other genetic forms of neutropenia.

Neutropenia was considered 'acute' if lasting <6 months and 'chronic' if lasting more.

For statistical analysis, we used standard parameters such as mean, median, range, s.d., Fisher's exact test, Student's t-test, and Kaplan–Meier test.

Results

We analyzed data from 104 patients. Fifty-seven (54.8%) were male and 47 (45.2%) female. Most of them were of Italian nationality (92.3%), except for 4 African children (2 Libyan, 1 Egyptian, 1 Somali), 2 from East Europe, 1 from Colombia, and 1 from India. The age at onset of neutropenia was notably early, 48% before the age of 1 yr, 24% between 12 and 24 months, 28% over 24 months (global range from 1 months to 17 yrs) (Fig. 1). Neutropenia was detected during evaluations for different clinical conditions: acute or recurrent infections were the main reasons (77%), while in 23% of cases, neutropenia was incidental.

Most patients showed a chronic course with persistence of neutropenia over 6 months (n = 66, 63.5%). In these patients, follow-up period ranged between 7 and 84 months (mean 23.7 months, median 15 months), while in acute forms, it was extended until 1 month after resolution. The etiologies of acute and chronic neutropenia in our cohort are shown in Table 1.

Acute neutropenia (n = 38) was mainly due to infections (n = 26, 68.4%), while one-third remained of unknown etiology.

Post-infectious neutropenia was diagnosed in patients with clinical and biochemical features of infection who showed a reduction in ANC during their acute illness (n = 28). Neutropenia in this group was frequently severe (50%) or moderate (36%). The responsible pathogen was identified in half of the patients (Table 2). Among them, almost all (n = 13) had viral infection, mainly from herpes viruses spp, with positive titers of specific IgM antibodies or positive PCR on blood/serum, and one patient had bacterial infection due to *Neisseria meningitidis*. In half of patients, no infectious agent was identified, although a bacterial origin was suggested on the basis of clinical and laboratory findings. Only in two patients, both infected by parvovirus B19, neutropenia lasted more than 6 months, and in one of them, it resolved after IVIg treatment.

Three patients experienced drug-induced neutropenia after treatment with ganciclovir for CMV congenital infection. One of them, who accidentally received drug overdose, showed chronic neutropenia lasting 8 months.

Among all chronic forms, the most frequent was chronic idiopathic neutropenia (CIN) (n = 33, 50%), followed by autoimmune neutropenia (AIN) (n = 22, 33.3%). The diagnosis of AIN was established after finding positive antineutrophil antibodies, while CIN was diagnosed by exclusion, after normal first- and second-level investigations. Neither physical
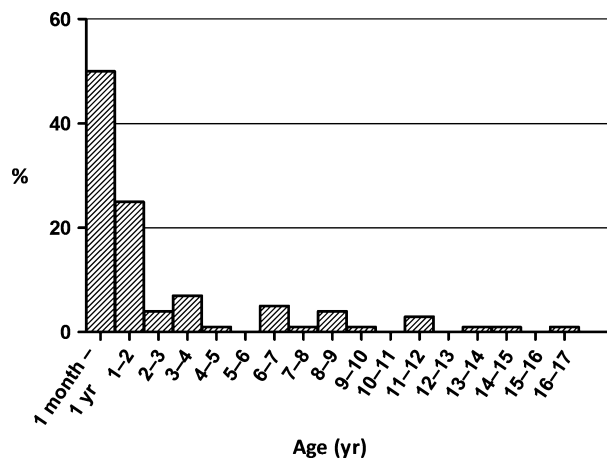
abnormalities (i.e., dysmorphic features, albinism, heart or skeletal anomalies, uropathy, etc.) nor signs/symptoms or laboratory data of a specific disorder were detected, thus

Table 2 Characteristics of Post-infectious neutropenia

Pt	Infection	Age at diagnosis (months)	ANC at diagnosis (/µl)	Duration of neutropenia (months)
Known pathogen				
1	HHV-6	11	700	0.5
2	HHV-6	3	100	0.25
3	HHV-6	18	330	2.5
4	HHV-6	12	300	5
5	HHV-6+ CMV	5	210	3
6	HHV-6+ EBV	36	1000	0.3
7	EBV	9	520	3
8	EBV	168	820	2.6
9	VZV	43	1200	0.5
10	VZV	1.5	440	3.5
11	HSV	13	400	0.6
12	*Neisseria meningitidis*	96	1100	2
13	Parvovirus B19	96	830	>6*
14	Parvovirus B19	72	420	>6*
Unknown pathogen				
1	Upper respiratory infection	12	165	1
2	Upper respiratory infection	13	490	0.1
3	Upper respiratory infection	8	830	0.5
4	Upper respiratory infection	6	380	6
5	Upper respiratory infection	108	970	0.25
6	Upper respiratory infection	12	490	0.6
7	Isolated fever	25	1420	0.5
8	Isolated fever	3	520	5
9	Isolated fever	12	380	0.2
10	Urinary tract infection	15	840	3
11	Urinary tract infection	4	210	1.5
12	Sepsis	10.5	920	1.5
13	Sepsis	6	190	2
14	Arthritis	2	890	1

*The two patients infected by parvovirus B19 showed chronic neutropenia.

Figure 1 Age distribution at onset of neutropenia.

Table 1 Etiologies of acute and chronic neutropenia

Acute	N	%	Chronic	N	%
Post-infectious neutropenia	26	68.4	Chronic idiopathic neutropenia	33	50
Idiopathic neutropenia	10	26.3	Autoimmune neutropenia	22	33.3
Drug-induced neutropenia	2	5.3	Congenital neutropenia	6	9
			Benign familial neutropenia	2	3
			Post-infectious neutropenia	2	3
			Drug-induced neutropenia	1	1.5
Total	38	100	Total	66	100

excluding forms of neutropenia associated with syndromes or other diseases (i.e., metabolic). Overall, 32 of 55 (58%) patients with AIN and CIN underwent bone marrow aspiration for morphology and, in some cases, also for cytogenetic, immunophenotyping, and virologic. In AIN, bone marrow resulted normal or rich with granuloblastic hyperplasia, while in CIN, a normal bone marrow morphology predominated. In particular, 20 of 33 CIN patients were tested for bone marrow. The other 13 patients were not tested either because neutropenia eventually resolved (n = 6), patient's parents did not agree with aspiration (n = 2), patients were lost to follow up (n = 3), or the exam was not performed yet at time of the study analyses (n = 2).

Congenital neutropenia was diagnosed in 6 children (Table 3). In 3 patients, severe congenital neutropenia (SCN) was identified by molecular analysis of *ELANE* gene. The other 3 patients were, respectively, diagnosed with X-linked hyper-IgM syndrome (CD40L mutation), methylmalonic aciduria, and suspected Cohen syndrome.

Benign familial neutropenia was diagnosed in two patients, based on their ethnicity, the relatively mild level of neutropenia, and a similar reduction in ANC detected in their parents.

Globally, in the whole cohort, at the time of first detection, neutropenia was more frequently severe or moderate than mild (severe n = 42, 45%; moderate n = 40, 43%; mild n = 11, 12%). In 11 patients, onset data were not available (onset ANC not specified in patient's history). The etiologies of neutropenia in children with a ANC $<0.5 \times 10^9$/l at first evaluation are shown in Fig. 2: One-third had post-infectious neutropenia, the others were almost all affected by acquired chronic forms CIN and AIN, and only two patient were diagnosed with congenital neutropenia (one SCN and one methylmalonic aciduria). Indeed, 4 of 6 patients with congenital neutropenia (including two with *ELANE* mutation) had ANC above 0.5×10^9/l on initial evaluations. The acquired chronic forms, CIN and AIN, presented with ANC above 0.5×10^9/l, respectively, in 60.7% and 26.3% of patients (Fig. 3).

Table 4 summarizes demographic and laboratory data of the 55 patients with AIN and CIN. The mean age at onset was 20 months (range 2–156) in AIN and 31 months (range 1–141) in CIN. The ANC at onset of neutropenia was different between the two groups with a mean of 314 µl (range 100–700) in AIN vs. 518 µl (range 10–1270) in CIN (p = 0.01). The average follow-up period for AIN and CIN patients was 25

and 20 months, respectively. In particular, 63.6% of AIN patients and 57.6% of CIN patients were followed up beyond the completed second year of age. Remission of neutropenia was observed in both groups, but AIN patients showed a lower remission rate during a 24-month follow-up (p = 0.027) (Fig. 4). Among patients who recovered (n = 25; AIN = 8 and CIN = 17), the duration of neutropenia was 19.6 months (range 7–37) for AIN and 15.4 months (range 8–46) for CIN patients.

In terms of clinical course, only 13 patients with CIN and AIN (23.6%) experienced infectious episodes during follow-up (Fig. 5). The most common site of infection was upper respiratory tract (n = 11, 39.3%). Other infections included lower respiratory tract (n = 4, 14.3%), cutaneous abscess
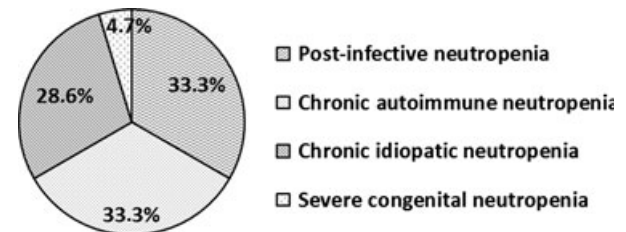
Figure 2 Etiologies of neutropenia in patients with ANC $<0.5 \times 10^9$/l at first evaluation (n = 42).
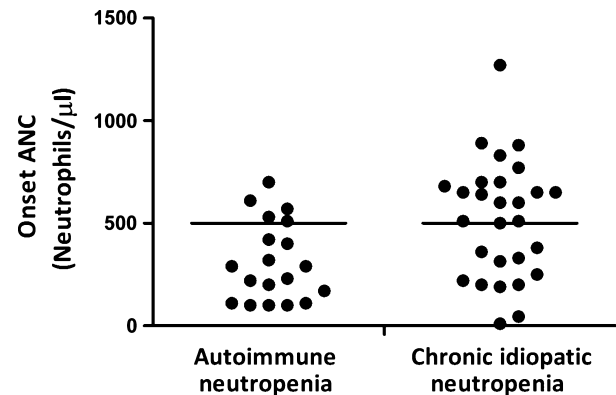
Figure 3 Onset ANC of patients with AIN and CIN: above 0.5×10^9/l, respectively, in the 26.3% and 60.7% of patients. Data were not available from 3 patients with AIN and 5 patients with CIN.
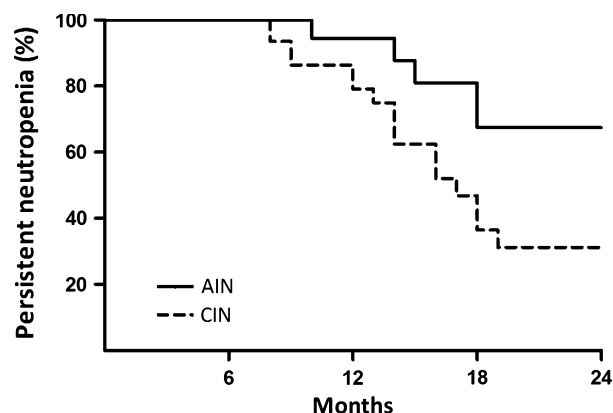
Table 3 Characteristics of congenital neutropenia

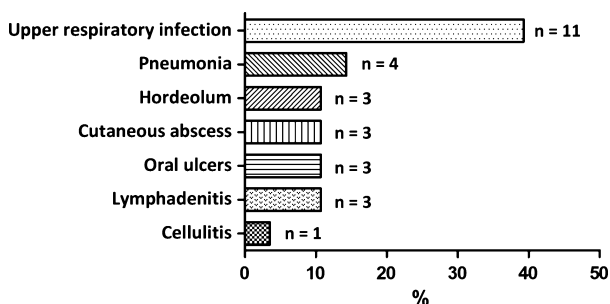| Pt	Diagnosis	Gene mutation	Age at onset (months)	ANC at onset (/µl)	Mean ANC during follow-up (/µl)	Treatment with G-CSF
1	SCN	*ELANE*	1	690	642	Yes
2	SCN	*ELANE*	9	320	440	Yes
3	SCN	*ELANE*	1	720	1360	No
4	Hyper-IgM syndrome	*CD40L*	42	680	1300	No
5	Methylmalonic aciduria	ND	1	360	1640	No
6	Suspected Cohen syndrome	Molecular analysis ongoing	2.3	590	1580	No

ND, not done.

Table 4 Characteristics of autoimmune neutropenia (AIN) and chronic idiopathic neutropenia (CIN)

Parameter	Autoimmune neutropenia (AIN)	Chronic idiopathic neutropenia (CIN)
Total patients	22	33
Sex male/female	8 (36.4%)/ 14 (63.6%)	15 (45.5%)/ 18 (54.5%)
Age at onset (mean, range)	20 months (2–156)	31 months (range 1–141)
ANC at onset (mean, range)*	314 µl (100–700)	518 µl (10–1270)
ANC during follow-up (mean, range)	712 µl (80–2920)	814 µl (45–3440)
ANC nadir	80 µl	10 µl
Follow-up period (mean, range)	25 months (6–84)	20 months (8–73)
Patients with follow-up beyond the second year of age	14 (63.6%)	19 (57.6%)

*$p = 0.01$.

Figure 4 Remission rate of neutropenia in patients with AIN and CIN during a 24-month follow-up: AIN patients showed a lower remission rate ($p = 0.027$).

Figure 5 Location and frequency of infections in patients with AIN and CIN during follow-up (n = 13).
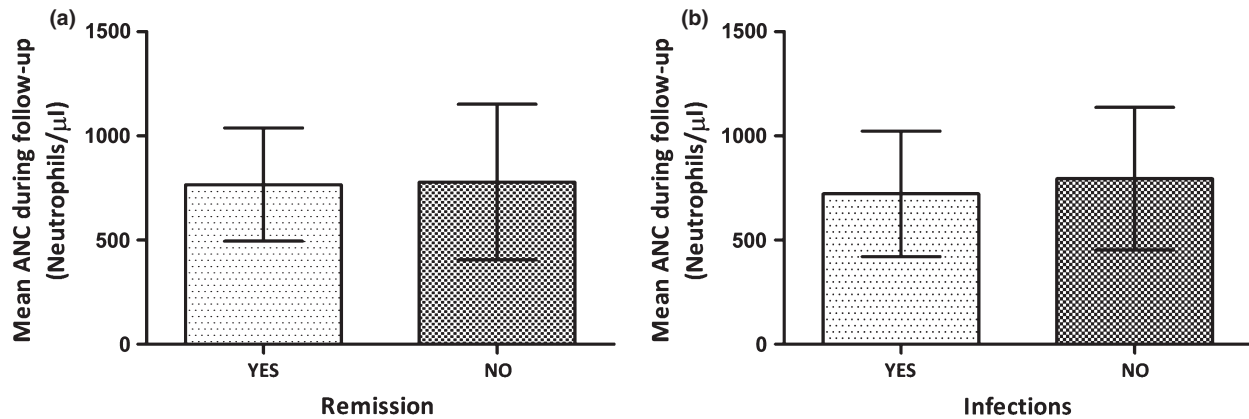
Discussion

The widespread use of routine biochemical assay has led to increased findings of neutropenia in pediatric practice. A special feature is that neutropenia is in fact a laboratory data, before representing a disease itself, and its origin and significance are extremely variable. Neutropenia may represent a predisposing factor to severe and life-threatening infections, as it is well known for patients with malignancies (15), but it can even be diagnosed incidentally in asymptomatic children, as complete blood count (CBC) is widely performed in outpatient settings.

Compared with the previous cohorts (4, 11, 18, 21), our populations includes a high proportion of patients with chronic neutropenia (63.5%). Chronic neutropenia encompasses a wide spectrum of conditions, either as an isolated disorder or as a part of a syndrome (16). Patients with chronic idiopathic neutropenia and autoimmune neutropenia constitute the largest number of patients in this series, in addition to a number of less common forms such as severe congenital neutropenia, primary immuno-deficiency, metabolic disorder, and inherited syndromes.

CIN and AIN have a similar clinical presentation and course. They both can be completely asymptomatic or lead to recurrent infections, often mild (5, 7). Only the detection of antineutrophil antibodies allows differential diagnosis, but they are not always searched in clinical practice, and furthermore, their detection presents technical difficulties (19, 20, 23). Some authors hypothesized that part of CIN patients could be affected by a misrecognized AIN (7, 22, 24). This hypothesis is supported by our experience: The systematic research of antineutrophil antibodies in 55 patients with isolated chronic neutropenia revealed 22 autoimmune forms (40%). Such a prevalence is more frequent than previously reported (5, 7, 12). Nevertheless, in the present study, the two groups showed subtle different features: Children with AIN usually presented with a lower ANC at onset and showed a lower remission rate during a 24-month follow-up. About this latter data, previous studies reported that AIN patients often spontaneously recover at the age of 2–3 yrs (9, 19, 20). As in the present study, only the 63.6% of patients with AIN were followed up beyond 2 yrs of age, it is possible that a longer follow-up could have shown a higher remission rate in this patients group. Prolonged treatment with G-CSF was administered only to 7 patients with CIN or AIN, and all responded with elevated neutrophil count. A substantial number of our CIN/AIN patients did not fulfill the strict criteria for the enrollment in

(n = 3, 10.7%), hordeolum (n = 3, 10.7%), stomatitis/oral ulcers (n = 3, 10.7%), and lymphadenitis (n = 3, 10.7%). One patient (3.5%) presented with cellulitis. Severe infections requiring hospitalization occurred rarely. No patients with either AIN or CIN suffered from long-term consequences after infections. No significant difference was noticed in terms of mean ANC between patients with and without remission of neutropenia (respectively, 766 µl and 778 µl), nor between patients with and without infections during follow-up (respectively, 721 µl and 794 µl) (Fig. 6). Forty-five of 55 AIN/CIN patients were observed clinically without G-CSF treatment, while the remaining 10 patients were treated with G-CSF on the basis of their history of frequent or severe infections, with good clinical response (three of them received G-CSF only on demand). None of the patients was on antibiotic prophylaxis.

Figure 6 Mean ANC of patients with AIN and CIN during follow-up: No significant difference in ANC values was noticed between patients with and without remission of neutropenia (a), nor between patients with and without infections (b) during the study period. Bars indicate s.d.

the International Registry of Severe Chronic Neutropenia (SCNIR), showing ANC at onset $>0.5 \times 10^9$/l (60.7% of CIN and 26.3% of AIN) and a benign clinical course with few recurrent infections and frequent spontaneous remission.

In an effort to evaluate the clinical significance of neutropenia, we further analyzed the relations between ANC values and etiology, duration of neutropenia or infectious episodes during follow-up.

Severe neutropenia with ANC $<0.5 \times 10^9$/l is a reason of concern and may be suspicious for congenital forms. However, in our experience, 4 of 6 patients with congenital neutropenia (including two with *ELANE* mutation) had ANC above 0.5×10^9/l on initial evaluations. On the other hand, one-third of patients with neutrophil level below 0.5×10^9/l at onset were diagnosed with a post-infectious acute form.

In the context of CIN and AIN, we further analyzed the mean ANC of patients in relation to infectious episodes and remission of the defect during follow-up. Patients with infections had mean ANC values comparable to asymptomatic patients, as well as patients who presented long-term remission had mean ANC values comparable to those with persistent neutropenia. Although the mean ANC does not take into account possible fluctuations of neutrophil number, which could partially affect these results, we could not demonstrate a direct and strong correlation between ANC and infections or ANC and long-term remission.

Acute neutropenia occurred in approximately one-third of our patient. An infection was the main reason for a transient defect, mainly by viral agents. Neutropenia in this group was frequently severe, in contrast to what previously reported (6). It is worth to point out that an infection can represent both the cause (post-infectious neutropenia) and the consequence (infection in a neutropenic patient) of neutropenia. Distinguishing these conditions could not be simple at first observation, but little anamnestic information (previous CBC and history of infections), some microbiological analysis, and observation of patient's ANC in the subsequent few months may help to define the diagnosis.

In the present study, drug-related neutropenia was diagnosed in only three children. However, the role of drug toxicity is very

difficult to define, because the spectrum of potentially involved drugs is wide and it may also include unconventional drugs.

Regarding inherited neutropenia, there are currently several known causes that can be diagnosed at molecular level. In some cases, neutropenia is isolated (i.e., in patients with *ELANE* mutations), but in most of them, neutropenia is a part of a broader spectrum of signs and symptoms often involving extra-hematopoietic manifestations. Therefore, an accurate physical examination, including multidisciplinary evaluation, together with advanced laboratory tests and bone marrow analysis helps physicians to exclude or identify the majority of the known genetic forms of neutropenia. As suggested by the consensus guidelines on diagnosis from the Neutropenia Committee of the Marrow Failure Syndrome Group of the AIEOP (16), considering that chronic idiopathic neutropenia is an disorder of granulopoiesis characterized by prolonged neutropenia in the absence of any apparent underlying etiology, CIN patients should be placed on a monitoring program, and a diagnostic revaluation should be performed in case new elements suggestive of other diagnosis arise. In the future, the differential diagnosis of chronic idiopathic neutropenia will include a broad spectrum of genes, including recently identified genes. New approaches based on next-generation sequencing will eventually be adopted on a wider basis to facilitate the diagnosis of these patients. This will require an extensive validation of these new techniques and careful evaluation of the cost-benefit of this approach.

Considering the results of our study, it is worth to point out several limitations. Because of the high specialization of our Unit of Immunology and Infectious Disease and Unit of Hematology, it is likely that the sample study is not representative of the general pediatric population. The study was partially retrospective and little information may not be complete, depending on the compilation of medical records. Furthermore, we had to exclude patients with incomplete follow-up, who were likely affected by acute neutropenia (some did not return to visit after finding a normal ANC in outdoor exams). Our data were derived from a single tertiary care setting and cannot be extrapolated to an outpatient setting; thus, they reflect significant ascertainment bias inherent in any

single institution study. These factors are likely responsible for the prevalence of chronic neutropenia in our cohort, in contrast to the previous series (4, 11, 18, 21). Another limitation comes from the age distribution of our cohort, with a high prevalence of infants (n = 50, 48%). Before the age of 1 yr, neutropenia is defined with ANC $<1 \times 10^9$/l, while the severity classification distinguishes between mild, moderate, and severe neutropenia according to ANC values starting from 1.5×10^9/l (1). Therefore, neutropenic infants were only classified as moderate or severe defects. This could explain the higher prevalence of severe neutropenia in our cohort. Further studies focusing on neutropenia in infants are needed to identify a suitable classification for this age group.

In conclusion, our study confirms the great heterogeneity of diseases underlying neutropenia in children, although the frequency of the different etiologies observed in our patients could not reflect the real distribution of the causes in the general pediatric population. In our experience, we could not demonstrate a correlation between ANC level at onset and the nature of the underlying disorder. Similarly, ANC did not appear useful in predicting susceptibility to infections or long-term remission in patients with chronic acquired neutropenia. Neutropenia remains a disease of concern to pediatricians, requiring several laboratory investigations, prolonged follow-up, and in few cases, advanced molecular methods. Future prospective and structured studies are required to better assess the prevalence of different forms of neutropenia in general pediatric population.

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Conflict of interest

The authors have no conflict of interest to declare.

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