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RESEARCH ARTICLE

Idiopathic neutropenia of infancy: Data from the Italian Neutropenia Registry

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Abstract

Autoimmune neutropenia of infancy (AIN) is characterized by low risk of severe infection, tendency to spontaneously resolve and typically onset at ≤4–5 years of age; it is due to auto-antibodies whose detection is often difficult. In case of negativity of 4 antineutrophils

Justification of the high number of authors: this is a registry study and a lot of researchers and physicians contributed to the enrollment of patients and data analysis.

autoantibody tests, after having excluded ethnic, postinfection, drug induced, or congenital neutropenia, according to the Italian guidelines the patients will be defined as affected by "idiopathic neutropenia" (IN). We describe the characteristics of 85 IN patients enrolled in the Italian neutropenia registry: they were compared with 336 children affected by AIN. The 2 groups were clinically very similar and the main differences were detection age (later in IN), length of disease (longer in IN) and, among recovered patients, age of spontaneous recovery: the median age at resolution was 2.13 years in AINs and 3.03 years in INs (P = .00002). At bivariate analysis among AIN patients earlier detection age (P = .00013), male sex (P = .000748), absence of leucopenia (P = .0045), and absence of monocytosis (P = .0419) were significantly associated with earlier recovery; in the IN group only detection age (P = .013) and absence of monocytosis (P = .0333) were significant. At multivariate analysis detection age and absence of monocytosis were independently significant (P = 6.7e-05 and 4.4e-03, respectively) in the AIN group, whereas in the IN group only detection age stayed significant (P = .013).

1 | INTRODUCTION

Neutropenia is characterized by a reduced absolute neutrophil count (ANC). Among Caucasians the lower normal limit of ANC in children up to the age of 1 year is 1.0×10^9/L, whereas from >1 year to adulthood this limit is 1.5×10^9/L; neutropenia is defined as mild if ANC is between 1.0 and 1.5×10^9/L, moderate if between 0.5 and 1.0×10^9/L, and severe if $<0.5\times 10^9$/L.[1] Autoimmune neutropenia of infancy (AIN) is characterized by a low risk of bacterial infection,[2–4] a tendency to spontaneous resolution[2–4] and typical occurrence under the age of 4-5 years.[2–5] AIN is due to auto-antibodies against human neutrophil antigens (HNAs) but the detection of these autoantibodies is challenging with reliable expertise restricted to few specialized laboratories.[6] The direct test (to discover antibodies anchored on the patient's neutrophils), even though its reliability can be improved with some measures,[7] presents a high number of false positives. On the contrary, the indirect test (detecting in the patient's serum antibodies reacting with donor neutrophils) has a significant frequency of false negatives.[2,4,8] The worldwide most used technique is the granulocyte *immunofluorescence* test (GIFT),[2,6,9] but, cause its low sensitivity, some laboratories[6,9] also use the granulocyte agglutination test (GAT), which is generally less sensitive than GIFT,[2] and the monoclonal antibody immobilization of granulocyte antigens, a more laborious and time consuming technique whose sensitivity, according to some reports,[10] seems to be lower than in the GIFT. To overcome the sensitivity limits of GIFT techniques such as mixed-passive hemagglutination (based on the spontaneous sedimentation of indicator cells coated with antihuman immunoglobulin G (IgG), over a monolayer of fresh granulocytes),[11] transfected cell lines expressing neutrophil antigens,[12,13] soluble recombinant HNA production by transfection of insect cells[14,15] (based on recombinant HNA isolated from culture supernatant of transfected insect cells), bead-based antibody detection methods[16,17] (coated with specific neutrophils' antigens) or extracted granulocyte antigen immunofluorescence assay (EGIFA),[18] a new technique based on HNA antigens immobilized with monoclonal antibody-conjugated microspheres, have been proposed but they are cumbersome and have not yet clearly proved their reliability; furthermore most of them are not yet commercially available. Therefore most laboratories continue to rely on GIFT, also based on the fact that its sensitivity definitely increases on repeated determinations.[4] Thus, in case of negativity of the first test and still withstanding the clinical suspicion of AIN, the Marrow Failure Group of AIEOP[19] (Italian Association of Pediatric Hemato-Oncology) in line with other groups[2,20,21] recommend repeating the test up to 4 or more times. Whenever all indirect testings remain negative and the clinical picture is consistent with that of AIN, then the children will be defined as suffering from "idiopathic neutropenia" (IN). All this taken together it looks possible that under the denomination of IN are included cases of AIN that are not correctly diagnosed because of the limited usefulness of the key diagnostic tests. In this study we analyzed the characteristics and the outcome of 85 IN children enrolled in the Italian neutropenia registry (INR) of AIEOP over a 16-year time-span and compared them to the largest ever-reported cohort of AIN children (336), who were enrolled in the INR in the same period.

2 | METHODS

2.1 | Data collection

Children diagnosed with AIN and IN included in the INR of AIEOP from January 1, 2002 to April 1, 2018 were considered eligible for the study. Diagnosis of AIN and IN was performed according to the guidelines published by our group.[19] In particular IN patients where those with neutropenia lasting more than 3 months, negative in at least 4 GIFTs and without other associated underlying disease. At least 3 normal ANC over 12 months were requested to address a definitive remittance. Informed consent for the collection of clinical data was obtained from the parents or legal guardians according to the Helsinki declaration and registry guidelines at the moment of enrollment in the Registry. INR institution was approved by the ethics committee of G. Gaslini Institute (Genova, Italy) that is the seat of the Registry. Anonymity was guaranteed by codifying data entry.

2.2 | Details of infections

Data on documented infections were collected from neutropenia onset until neutropenia recovery or last follow-up. Each infectious episode was reviewed and an infection was arbitrarily defined as "severe" in the presence of a final diagnosis of sepsis, pneumonia, skin/soft tissue abscesses, or meningitis/encephalitis according to previous literature[3]: other types of possible severe infections were evaluated on a case-by-case basis.

2.3 | Laboratory evaluation

Samples were analyzed in parallel in 3 different Italian laboratories located in Genoa, Turin and Milan. Detection of circulating antigranulocyte antibodies was performed by the indirect GIFT. A panel of purified granulocytes obtained by density gradient separation (Dextran and Ficoll) from healthy donors was used: the donors were unselected and not genotyped for HNA. Briefly, 2×10^5 paraphormaldeyde-fixed (1% for 2′) granulocytes from 4-10 healthy male donors (mean 6.77) were individually incubated with a pool of AB sera from nontransfused male donors (negative control), with patients' sera and with a positive control serum (30′ at 37°C). After washing with phosphate-buffered saline containing 0.1% NaN_3 and 1% fetal calf serum, cells were incubated with fluorescein isothiocyanate-labeled $F(ab')_2$ fragments of rabbit antihuman IgG (30′ at RT) and then acquired by a FACSCanto II flow-cytometer. GIFT was considered positive in the laboratory of Milan if the difference between the Median Channel of Fluorescence 1 (MCF-1) of negative control serum and patient's MCF-1 on the same donor's cells was equal to or greater than an internal cut-off value determined on a wide population of negative control sera (n = 300). In the laboratory of Genoa and Turin the test was positive if the mean fluorescence intensity was >2 SD of the mean of 1 hundred control sera from healthy subjects.

2.4 | Statistical analysis

Statistical analysis was performed by the open source software R.[23] The chi-square test for independence was used to compare categorical variables. Non parametric tests (Wilcoxon test for independent groups, Kruskal Wallis test) were used to compare distribution in smaller groups. Linear regression models were used for continuous variables, and general linear models for multivariate analysis. Kaplan-Meier curves and analysis were performed by the R package Survival.[24,25] Bivariate analysis was used to analyze potential factors affecting recovery, using recovery incidence curves based on the Kaplan-Meier estimator, and the log-rank test (for categorical variables) or a Cox proportional hazard model (for continuous variables). The following variables at presentation were considered as possible prognostic factors: age of neutropenia detection, sex, white blood cell count (WBC), leucopenia (below lower limit for age), absolute lymphocyte count (ALC), absolute monocyte count (AMC), monocytosis (>1.0 $\times 10^9$/L), ANC and thrombocytosis (for age). The prevalence of selective IgA deficiency (SIgAD) (confirmed in at least 2 dosages) and increased IgG for age was also evaluated. A multiple regression analysis was also performed by a Cox model, including all risk factors that were significant at the bivariate analysis. The same variables were evaluated using the rate of severe infections as outcome. As we observed a rather high prevalence of SIgAD in both AIN and IN groups, we also used an external control cohort consisting of 470 children (either hospitalized or in outpatient) to verify if SIgAD was significantly more frequent in neutropenic patients than in the general population. Differences were considered significant whenever P was < .05.

3 | RESULTS

3.1 | Characteristics at presentation

As shown in Table 1 the AIN and IN populations at presentation only differed regarding age at detection of neutropenia (0.8 years in AIN vs 1.2 years in IN; P = .00035) and age of diagnosis (1.1 years in AIN vs 2 years in IN; P = .00000008); both the differences were significant also when the analysis was restricted (Table 2) to recovered IN and AIN patients (P = .0003 and .00000005 respectively). The median and mean time from the first to the fourth test in INs were 72.00 and 73.16 days, respectively (range 9-136). All other presentation features that we analyzed were comparable in AIN and IN groups. More specifically, at onset no difference could be appreciated between AIN and IN patients in terms of WBC, leucopenia for age, ANC, neutropenia type (severe/moderate/mild), median AMC, monocytosis, ALC, lymphocyte subsets, thrombocytosis, severe infections, increased level of IgG and direct antiglobulin test (DAT) positivity.

The prevalence of SIgAD was 3.1% and 3.0% in AIN and IN patients respectively (P = .97), and both prevalences were significantly higher than what was observed in a group of 470 laboratory controls (0.21%, P = .00065 for AIN and P = .0040 for IN).

Positive DAT without any evidence of hemolysis was present in 4.4% of AIN and 3.1% of IN patients (P = .74); positivity of antinuclear antibodies or, less frequently, antismooth muscle antibodies or antineutrophil cytoplasmic antibodies, was appreciated in 4.5% of AIN and 2.4% of IN patients respectively (P = .37).

Bone marrow (BM) examination was done in 31.6% and 49.4% of patients of AIN and IN cohorts (P = .003). In all but 4 AIN patients it showed normal or increased cellularity with or without a relative paucity of the more mature stages of granulocyte development: in the remaining 4 children, all recovered from AIN, a moderate decrease of myeloid cellularity was observed.

3.2 | Outcome

The Kaplan Meier incidence of recovery curve for AIN and IN patients is shown in Figure 1. The expected incidence of recovery at 5 years follow-up was 87.12% in the AIN group and 81.28% in the IN group: the difference was not significant (P = .151).

In the group of recovered children (Table 2) 38.1% of AINs and 20.6% of INs had a disease duration of ≤12 months (P = .0099) and 86.0% and 76.2% recovered at ≤5 years of age (P = .062). When we analyzed the modality of recovery we found that in 77.8% of AIN and 75.0% of IN patients there was a sudden resolution (stable

TABLE 1 Comparison between pediatric AIN and IN

	AIN (336)	Idiopathic (85)	*P*
Sex (M%)	56.8%	50.6%	.29
Age at neutropenia detection (years, median)	0.8	1.2	.00035
Age at diagnosis (years, median)	1.1	2.0	.00000008
ANC (median) at onset	0.45×10^9/L	0.38×10^9/L	.47
Neutropenia type (severe/moderate/mild)	55.2%-37.6%-7.2%	60.0%-29.4%-10.6%	.28
WBC (median) at onset	6.1×10^9/L	5.7×10^9/L	.60
Leucopenia at onset	35.9%	42.4%	.27
AMC (median) at onset	0.62×10^9/L	0.61×10^9/L	.87
Monocytosis at onset	20.0%	29.3%	.08
ALC (median) at onset*	4.5×10^9/L	4.3×10^9/L	.16
Thrombocytosis at onset	11.1%	20.0%	.06
Increased IgG at onset	6.6%	5.9%	.83
SIgAD	3.1%	3.0%	.97
DAT+	4.4%	3.1%	.74
BM performed	31.6%	49.4%	.003
Severe infections	11.9%	11.8%	.97
G-CSF treatment	7.5%	2.8%	.29

Abbreviations: AIN, autoimmune neutropenia; IN, idiopathic neutropenia; ANC, absolute neutrophil count; WBC, white blood cell count; AMC, absolute monocyte count; ALC, absolute lymphocyte count; IgG, immunoglobulin G; SIgAD, selected IgA deficiency; DAT direct anti-globulin test; BM, bone marrow; G-CSF, Granulocyte colony stimulating factor.

maintenance of normal ANC after neutropenia period), whereas in the remaining children there was a transient intermittent neutropenia phase (alternation of normal and subnormal ANCs) lasting up to 3.5 years: in this group median time of definite recovery from the first normal WBC were 0.62 and 0.95 years in AIN and IN patients respectively (*P* = .013).

Overall 11.9% of the AIN and 11.8% of the IN patients (*P* = .97) suffered from severe infections without any reported long-term consequences. No cases of periodontitis, oral abscess, deep abdominal infections, fungemia, or otomastoiditis were reported. Antibiotic prophylaxis was never administered. Granulocyte colony stimulating factor (G-CSF) was administered (always "on demand") to 7.5% of the AIN and 2.8% of the IN patients, respectively (*P* = .29).

TABLE 2 Comparison between recovered pediatric AIN and IN

	AIN (226)	Idiopathic (63)	*P*
Age at neutropenia detection (years, median)	0.71	1.19	.0003
Age at diagnosis (years, median)	1.03	1.85	.00000005
Age at recovery (year, median)	2.13	3.03	.00002
Median duration of disease (years, median)	1.28	2.00	.000038
Median time of definite recovery in patients recovered after transient intermittent neutropenia phase (years, median)	0.62	0.95	.013
Sudden recovery	77.8%	75.0%	.65
Recovered patients with disease length ≤ 12 months	38.1%	20.6%	.0099
Recovery at <5 years of age	86.0%	76.2%	.062

3.3 | Factors affecting outcome

In the Kaplan-Meier analysis, among the possible prognostic factors, earlier age at detection of neutropenia (*P* = .00013), male sex (*P* = .00075), absence of leucopenia (*P* = .0045), and absence of monocytosis (*P* = .042) were associated with a significantly better recovery curve in the AIN group, whereas in the IN group only detection age (*P* = .013) and absence of monocytosis (*P* = .0333) were significant. A multivariate analysis by a Cox model in the AIN group, including all 4 variables that were significant at bivariate analysis, showed that only age at detection of neutropenia and absence of monocytosis were independently significant (*P* = 6.7e-05 and 4.4e-03, respectively). In the IN group, only detection age remained significant at multivariate analysis (*P* = .013).

None of the considered risk factors was statistically associated with a higher burden of infection.

4 | DISCUSSION

In literature there is an evident discrepancy of terminology about IN since patients who do not display any known cause of neutropenia are classified as affected from time to time not only by *IN* or *chronic IN*,[22,26–29] but also by *chronic IN syndrome*,[30] *chronic-acquired IN*[31] or *idiopathic chronic benign neutropenia*.[32] Furthermore a series of studies from Crete investigated local adult patients, originally defined as affected by *nonimmune chronic IN of adults*, for whom, actually, the term *idiopathic* could be misleading since some evidence about an immune mediate pathogenesis impairing the granulocytopoiesis have been reported[33,34]: it is not clear how much this pathogenic mechanism can be considered valid also in pediatric IN and/or INs of other ethnic groups. In our opinion and accordingly to other authors[22,28,35,36]

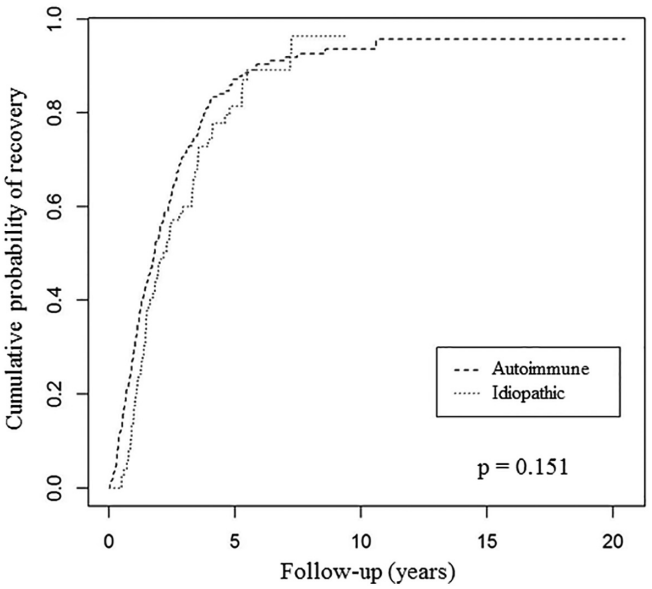

FIGURE 1 Kaplan–Meier recovery curve of autoimmune and idiopathic neutropenic patients

it should be better to more simply address every type of neutropenia eluding any specific diagnosis as "idiopathic". Since it is probable that, in childhood[8,36,37] as in adulthood,[38,39] a high percentage of these cases were autoimmune neutropenias in which, due to the low sensitivity of current tests, it is not possible to reach a firm diagnosis, we suggested,[19] in case of first negativity, to repeat the searching of indirect antineutrophil antibodies several times (at least 4) with the possible association of the other best techniques currently available. And so, as a consequence of Italian guidelines observance, this is the first study where all patients were classified as affected by IN on the basis of strictly homogeneous criteria (≥ 4 negative indirect GIFTs); furthermore this is one of the first papers focusing on IN of childhood, since in literature it is possible to find above all mixed cohorts where AIN and IN of infancy were analyzed together[40,41] or where neutropenias other than IN or AIN were also included.[27,42] To the best of our knowledge there are only 2 papers[21,37] where much smaller cohorts of idiopathic and autoimmune neutropenic children were compared and they are in partial agreement with our results, even though in both of them it was not reported how many times IN patients had been tested for autoantibodies searching. The oldest one[21] compared 70 antibody positive and 46 antibody negative children and found a significantly higher mean age at diagnosis (not at the detection of neutropenia) in the IN group (P = .035): the higher age at diagnosis is in agreement with our findings but it is of minor significance since in IN patients, where antibody searching is presumably performed more times (at least 4 in our IN group), the diagnostic process is longer. The second and most recent study,[37] comparing 36 antibody positive and 24 antibody negative children, addressed among these latter ones, in accordance to our analysis, an older median age at recovery even though, probably due to the low number of analyzed patients, this difference was not statistically significant. Actually the IN pathogenesis persists unexplained but this is the first study that addresses with reasonably large and solid data the debated issue of the overlap between AIN and IN in childhood. First, it is a fact that the large majority of IN patients in our study present, as in the AIN group, a spontaneous remittance: since among IN recovered patients post infection and drug induced neutropenias had been excluded, a pathogenic hypothesis other than undiagnosed AIN seems really difficult to postulate. Furthermore after having examined a large number of key features our analysis shows that AIN and IN cohorts have very comparable clinical presentation, infection load (type and number), prognostic factors, outcome including time and modalities of resolution and use of G-CSF. All these features, plus the correlation, in our INs as in AIN pediatric patients,[4,43] between younger age at appearance of neutropenia and absence of monocytosis with earlier recovery, the awareness that the detection of anti-neutrophil autoantibodies is depending on methods and contexts,[2,10] the reported evidence that no correlation can be found in AIN patients between disappearance of autoantibodies and time of recovery from neutropenia,[10] lead us, according to many other authors[2,22,26,27,32,42] to be firmly convinced that a vast percentage of INs, both in adulthood and in childhood, were AINs impossible to diagnose, probably for different antibody titers or avidity for the target antigen: this aspect poses the needs to make efforts to find effective disease specific diagnostic tests preferentially performed by highly specialized laboratories. In any case, even though the outcomes in both groups is pretty the same, we continue to suggest the searching of the anti-neutrophil autoantibodies in any case of suspected AIN since it is better for parents to receive a formal diagnosis for their child, and to be informed, in the light of the earlier recovery from an AIN than from an IN shown by the present analysis, that the neutropenia will probably disappear in few months.

Lower ANCs were associated to a greater disease seriousness in adult IN patients[39] but this feature was not present in our analysis where only 11.8% of children suffering from IN presented severe infection, none of them having any long-term consequences: monocytosis for age, less frequent in adult IN[20,22,30,35,38,39,44,45] than in our IN pediatric cohort, has been interpreted as possible compensatory anti-infection mechanism among AIN patients[46,47] and can possibly play a role in the low infectious burden presented by IN children. Furthermore the infrequency of severe infections in childhood seems to have an impact on the therapeutic strategy: none of IN (and AIN) patients enrolled in INR were continuously treated with G-CSF. On these basis, and accordingly to other expert clinicians,[36] it seems reasonable to suggest a treatment with G-CSF at minimal effective dosage only for the very small minority of pediatric AIN and IN patients presenting extreme recurrent fevers/infections and/or at least one previous severe infectious event. Another much debated point about IN and AIN pediatric patients is whether to use antibiotic prophylaxis or not. In discordance to what reported in other countries,[2,10] in Italy this approach is absolutely infrequent: the low incidence of severe infections in our AIN and IN cohorts seems to confirm that antibiotic prophylaxis is unnecessary in the vast majority of patients.

Since IN in childhood as in adulthood is a diagnosis of exclusion, it can be made only after a thorough search for other causes but it remains unsolved if this diagnostic pathway should include BM examination with possible cytogenetics: BM aspirate was done in 31.6% and 49.4% of patients in our AIN and IN cohorts respectively with a not surprising higher prevalence among INs (P = .03), since in this group of patients an *official* diagnosis has not been reached. Actually, it is a fact that BM examination was always uninformative and so,

according to our data, we suggest that especially in childhood, where hematologic malignancies as cause of isolated neutropenia are very infrequent,[48–50] if the clinical picture of IN is superimposed to that of AIN (appearance at <2-3 years of age, no other associated cytopenia, no severe infections in the medical record, no clinical or laboratory criteria for suspicion of leukemia or congenital neutropenia) it is possible to postpone the procedure until after at least 4 years of age or unexpected changes in peripheral counts or medical examination.

In conclusion we think that this study, whose main limitation is its retrospective registry nature, strongly suggests that AIN and IN are the same disease only differentiated by the failure to demonstrate anti-neutrophil antibodies in the IN group and that an idiopathic neutropenic child with all the characteristic of AIN needs consequently to be managed as a child affected by AIN.

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CONFLICT OF INTEREST

Nothing to report.

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