CORRESPONDENCE

Autoimmune neutropenia of infancy: Data from the Italian neutropenia registry

To the Editor: 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 greater than 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 less than 0.5×10^9/L [1]. Autoimmune Neutropenia of Infancy (AIN) is due to auto-antibodies against Human Neutrophil Antigens (HNA). HNA-1 (FcγIIIb) is the most frequently involved, mainly in its isoforms HNA-1a and HNA-1b. In this report, that is the second largest study ever conducted on AIN [2], we presented the clinical characteristics of the disease of 157 AIN patients from the Italian Neutropenia Registry of the Associazione Italiana di Onco-Ematologia Pediatrica (A.I.E.O.P.) and assessed the sensitivity of the indirect anti-neutrophil antibody test. The methods are described in the on-line Supporting Information 1.

Historically the reported prevalence of AIN is 1/100,000 children under 10-year-old [3], but this is probably an underestimation; in the analysis restricted to patients of the present cohort diagnosed in western Sicily the incidence was 1 out of 6,300 live births.

T1 Some characteristics of the study population are shown in Table I. The female/male ratio was 3.6/6.4. The median age at onset was 0.70 year (range 0.005–4.59): in 82% of the cases neutropenia appeared at up to 18 months of age. In three patients (1.9%) the onset was at under 1 month of age: alloimmune neonatal neutropenia was excluded on the basis of a negative cross match between maternal serum and paternal neutrophils. It has been reported [2] that the onset of AIN is not possible at less than 1 month of age. Actually there have been three published exceptions [4,5] and three patients in the present series, so we can say that the appearance at this age is unusual but not impossible.

The frequency of children who were born preterm and then developed AIN was 13.2%. Interestingly this figure is significantly higher ($P = 0.016$) than that observed (6.9%) in a cohort of 487 children consecutively hospitalized for various reasons during 2014 in a pediatric center of Sicily. This finding is in keeping with one possible pathogenic hypothesis: that AIN is due to immaturity of the suppressor systems and that spontaneous recovery corresponds to the full development of suppressor T-cell function. At onset, median ANC was 0.45 (range 0.0–1.45×10^9/L), and the neutropenia was severe in 56.0%, moderate in 38.2% and mild in 5.7%. In 29.3% of the patients neutropenia was diagnosed by chance: this is in line with the figure of 27% in another report [6], but higher than the classic study by Bux et al. (8%) [2]. Median WBC at onset was 6.1×10^9/L. Leucopenia for age and monocytosis were present in 41.7% and 19.3% of cases, respectively.

Bone Marrow (BM) examination was done in 54 patients (34%), and in all but 2 it showed normal or increased cellularity with or without a relative paucity of the more mature stages of granulocyte development: in 2 children a moderate decrease of myeloid cellularity was observed.

The prevalence of selected IgA deficiency (a condition predisposing to autoimmunity) was 3% and was significantly higher than that observed in a group of 470 laboratory controls (0.21%, $P = 0.001679$). Increased Immunoglobulin G level, a probable consequence of augmented immune stimulation, was observed in 6% of the 133 evaluable patients. Fifty-one AIN children underwent an extensive autoimmunity investigation: no positive case was observed.

At the time of the analysis 10/157 patients were lost at follow-up and 131 out of 147 (89.1%) recovered from neutropenia. The median age at resolution was 2.14 years with a median length of disease of 1.30 years: the Kaplan Meier recovery curve is shown in Fig. F1 1. In the group of recovered children 65.1% had a disease duration of ≤24 months and 89.9% recovered at ≤5 years of age; the remaining 10.1% had a spontaneous remission at 5.1–11.1 years of age.

When we analyzed the modality of recovery we found that in 67.4% there was a sudden resolution (stable maintenance of normal ANC after neutropenia period), whereas in 32.5% there was a transient intermittent neutropenia phase (alternation of normal and subnormal ANCs) lasting up to 24 months: in this group median time of definite recovery from the first normal WBC was 0.65 years, with a range of 0.15–2.11 (standard error of 0.48).

Overall 44.2% of the children were hospitalized for fever or ascertained infections but only 9.6% suffered from severe infections without any long-term consequences. Antibiotic prophylaxis was never administered. Granulocyte Colony Stimulating Factor (GCSF) was administered (always "on demand," for short periods and mainly in the case of severe infections) to 7.1% of the patients.

Among the parameters analyzed in the Cox model only early age at onset ($P = 0.0001873$) and absence of monocytosis ($P = 0.009641$) were associated with a significantly earlier recovery. A lower age at presentation was also associated with a reduced length of disease ($P = 0.028$).

TABLE I. Clinical Characteristics of the Patients

	Autoimmune neutropenia of infancy (157)
Male	64.3%
Median age at onset (years)	0.70
Median age at diagnosis (years)	1.06
Median age at resolution	2.14
Median duration (years)	1.30
Recovery	89.1%
Median WBC at onset ($\times 10^9$/L)	6.1
Median ANC at onset ($\times 10^9$/L)	0.45
Leucopenia at onset	41.7%
Monocytosis at onset	19.3%
Increased IgG at onset[a]	6.0%
Selected IgA deficiency[a]	3%
Severe infections	9.6%

[a] Data available on 133/157 patients.

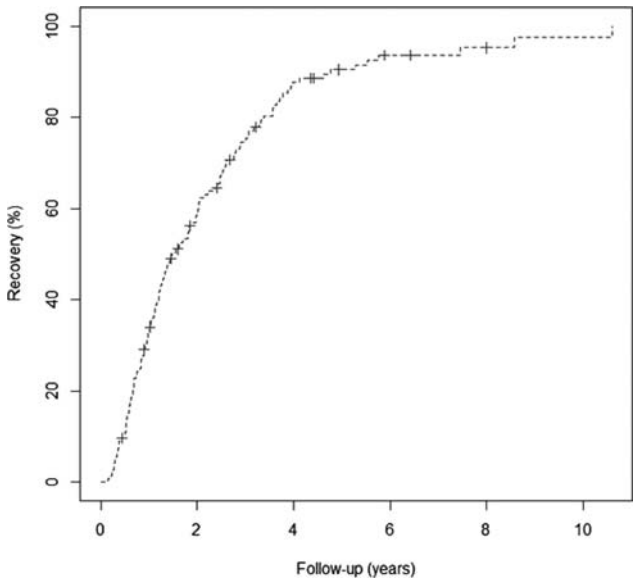

Figure 1. Kaplan Meier recovery curve. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Diagnosis of AIN is frequently troublesome. The direct test for anti-neutrophil auto-antibody detection has an elevated rate of false positives, and the indirect test has elevated false negatives [2]. We assessed the sensitivity of the Granulocyte Immunofluorescence Test (GIFT), after 1, 2, 3, and 4 assays: detection of circulating anti-granulocyte antibodies was always performed with unselected donors (non-genotyped for HNA). As shown in on-line Table I in Supporting Information the sensitivity of the test increased from 61.8% at the first determination to 81.8% at the fourth, thus supporting the hypothesis that repeated testing may remarkably improve the power of this diagnostic tool.

In conclusion our report after nearly two decades provides an update of the clinical presentation and outcome of AIN, which appears as a substantially benign and self-limiting condition although remission may occur even after long-term course in late pediatric age. Furthermore this study offers some new clinical insights such as a higher incidence in preterms and frequent recovery pattern consisting of alternating normal and neutropenic values.

Acknowledgments

ERG spa, Rimorchiatori Riuniti, Cambiaso & Risso, SAAR Depositi Oleari Portuali, UC Sampdoria are acknowledged for supporting the work of the Clinical and Experimental Hematology Unit of G. Gaslini Institute. No specific funding was received for this study. The Sicilian Primary Immunodeficiency Association is acknowledged for

J_ID: AJH Customer A_ID: AJH24187 Cadmus Art: AJH24187 Ed. Ref. No.: AJH-15-0928 Date: 18-September-15 Stage: Page: 2

supporting the work of the Pediatric Oncology-Hematology Unit of A.R.N.A.S. Civico Hospital. No specific funding was received for this study.

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Additional Supporting Information may be found in the online version of this article.

Conflict of interest: Nothing to report.

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Received for publication: 6 September 2015; *Accepted:* 9 September 2015
Published online: 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com)
DOI: 10.1002/ajh.24187

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