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Chronic benign neutropenia among Chinese children

華裔兒童所患的慢性良性嗜中性白血球減少症

Objective. To delineate the clinical behaviour of chronic benign neutropenia in Chinese children in Hong Kong.
Design. Retrospective study.
Setting. University teaching hospital, Hong Kong.
Patients. All infants and children with absolute neutrophil count of 1.5 x 10^9 /L or lower for more than 3 months.
Main outcome measures. Development of significant infection, and achievement of remission.
Results. Twenty-four children with chronic benign neutropenia were identified between 1992 and 2001. Their median age of diagnosis was 9 months. The mean (standard deviation) initial absolute neutrophil count was 0.28 x 10^9 /L (0.24 x 10^9 /L). Twenty-three patients presented with infection. Of the 19 patients tested, four (21%) were positive for anti-neutrophil antibodies. Bone marrow examination was performed in 17 patients: nine had normal results, but six showed evidence of peripheral consumption, one showed late maturation arrest at band stage, and one showed phagocytosis of myeloid cells by histiocytes. The overall hospitalised infection rate was 51.6 episodes per 1000 patient-months. Ten percent of cases were considered 'significant' infections and required hospital admission with either surgical intervention or intravenous therapy (antibiotics or fluid replacement). In the first year of diagnosis, more than 80% of patients had their lowest absolute neutrophil count (mean, 0.16 x 10^9 /L; standard deviation, 0.11 x 10^9 /L). Granulocyte-colony stimulating factor was used to treat three patients and induced transient elevation of absolute neutrophil count in all three. The projected remission rate was 55.4% at 3 years. Even for those with persistent disease, there was significant recovery in absolute neutrophil count to a mean of 0.5 x 10^9 /L (P<0.01).
Conclusions. Patients with chronic benign neutropenia experienced a relatively benign clinical course regardless of their remission status. Only a small proportion of patients developed significant infections. A multi-centre prospective study may help identify predictive factors of remission.

目的：描述香港華裔兒童所患的慢性良性嗜中性白血球減少症的臨床徵狀。
設計：回顧研究。
安排：一所大學教學醫院，香港。
患者：超過三個月嗜中性白細胞絕對數量為每升血液 1.5 x 10^9 個或以下的嬰兒和兒童。
主要結果測量：嚴重感染和緩解進展。
結果：1992至2001年間，共有24位兒童確診患上慢性良性嗜中性白血球減少症，接受診斷時的年齡中位數為9個月大。嗜中性白細胞絕對數量的平均值最初為每升血液 0.28 x 10^9 個（標準差為 0.24 x 10^9 個）。23位呈感染徵狀。在接受測試的19位兒童中，4人（佔21%）對於抗嗜中性白細胞抗體呈陽性反應。17位患者接受骨髓檢測：9人結果正常，6人有 peripheral consumption，1人顯示 band stage 遲緩成熟中止，1人出現組織細胞吞噬骨髓細胞的情況。住院期間感染的整體比率為每 1000 patient-months 51.6 段次，當中一成的病例屬「嚴重」，須留院接受手術或靜脈輸液治療（抗生素或補液）。在第一年的診療中，超過八成患者的嗜中性白細胞絕對數量是最低的（平均值為每升血液 0.16 x 10^9 個；標準差為 0.11 x 10^9 個）。3位患者接受粒細胞集落刺激因子法治療，誘發嗜中性白細胞絕對數量短暫回升。隨訪期第三年的推斷緩解率為55.4%。即使是病症頑固的患者，嗜中性白細胞絕對數量亦顯著回升至平均值每升血液 0.5 x 10^9 個（P<0.01）。

Key words:
Autoimmune diseases;
Chinese;
Immunoglobulins;
Neutropenia

關鍵詞：
自身免疫疾病；
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結論：不論緩解情況，慢性良性嗜中性白血球減少症患者病情的發展普遍屬良性，只有少數病人出現嚴重感染。跨中心的前瞻研究有助確定緩解的預後因素。

Introduction

Chronic benign neutropenia (CBN) of infancy and childhood was first described by Hotz and Fanconi in 1941 as described by Dale.[1] Subsequently, Zuelzer and Bajoghli[2] defined it as "a chronic state of mature neutrophil depletion with a compensatory increase in the immature granulocytes in the bone marrow analogous to erythroid hyperplasia in haemolytic anaemia". The condition actually encompasses two groups of disorder—namely, autoimmune neutropenia (AIN) and chronic idiopathic neutropenia (CIN). So far, there has been no universally agreed nomenclature and classification for chronic neutropenia in children.

Autoimmune neutropenia is defined as the presence of anti-neutrophil antibodies. Its incidence is approximately 1 in 100 000 children.[3] The largest series (240 patients with AIN) was reported by Bux et al[4]: the typical age at diagnosis among the patients was 5 to 15 months, and the majority (>90%) of patients had only benign infections, despite the severe neutropenia. Spontaneous remission was observed within 24 months; symptomatic treatment with antibiotics was sufficient in most cases, and granulocyte-colony stimulating factor (G-CSF) was indicated only under special circumstances. Similar observations have been made by Lalezari et al[5] in a series of 119 infants and children with AIN. Chronic idiopathic neutropenia shares a similar clinical course with AIN, differing only in the absence of anti-neutrophil antibodies.[1] In fact, because tests designed to detect antibodies to neutrophils can be non-specific and often unavailable, differentiation between CIN and AIN can be difficult.[6]

In this study, we reviewed our experience on CBN (ie AIN and CIN) among infants, and attempted to delineate its clinical course among local Chinese children.

Methods

A retrospective review of all Chinese patients who received a diagnosis of chronic neutropenia between 1992 and 2001 was performed in the Department of Paediatrics and Adolescent Medicine of the Queen Mary Hospital. Chronic neutropenia was defined as having an absolute neutrophil count (ANC) of 1.5 x 10^9 /L or lower for at least 3 months. For patients who presented with neutropenia for more than 3 months, initial investigations included determination of the complete blood picture twice a week for 4 weeks, immunoglobulin profiling, measurement of the level of anti-neutrophil antibodies, and bone marrow examination. Patients were followed up monthly in the initial 6 months to reach a definitive diagnosis. They were subsequently reviewed regularly at 6- to 9-month intervals through clinical assessment and determination of the complete blood picture. Additionally, the patients and their parents were instructed to return to the out-patient clinic or emergency room of our hospital for assessment when they had a fever or other symptoms suggestive of infection.

Records of patients with chronic neutropenia diagnosed during the 10-year study period were retrieved. We excluded all patients with congenital neutropenia, cyclic neutropenia, neutropenia 'secondary' to allo-immunity, or other immune or systemic diseases, because the aetiologies, clinical manifestations, natural courses, and prognoses of these disease entities were different from those of CBN.[6-9]

In general, the categorisation of chronic neutropenia was based on the time of onset, the pattern of variation in neutrophil levels in the blood, and the presence or absence of auto-antibodies. We followed the diagnostic criteria suggested by Dale et al[6] for congenital neutropenia, cyclic neutropenia, and CIN, and criteria suggested by Bux et al[4] for AIN. Congenital neutropenia was usually recognised from birth by the presence of severe infection, severe neutropenia (ANC of <0.5 x 10^9 /L), and bone marrow showing a maturation arrest of neutrophil production at an early stage. Cyclic neutropenia was generally presumed to be present if there were oscillations of blood neutrophil count in a cycle of 21 days and if patients were prone to develop severe infections during periods of severe neutropenia. Although no operational definition could be found for virus-induced neutropenia, none of the patients showed any clinical evidence suggestive of an obvious viral cause (eg viral hepatitis). Autoimmune neutropenia was defined as neutropenia in the presence of anti-neutrophil antibody, as detected by an assay described previously by Rose et al.[10] The limitation of the assay was that its specificity was unknown. Chronic idiopathic neutropenia was a diagnosis by exclusion and was defined as chronic neutropenia of unknown origin with which no other pathology could be associated.[11]

A total of 24 patients were identified during the study period. The total observation time was 1356 patient-months up to the time of chart review, and the median follow-up duration per patient was 56.5 months (range, 8.0-118.0 months). The clinical features, serial neutrophil counts, results of other investigations, and the use of G-CSF were examined. Granulocyte-colony stimulating factor has been shown to be useful in inducing temporary remission of neutropenia.[4] Furthermore, long-term safety of G-CSF has been shown in patients with severe congenital neutropenia, and in early 1990s, it was used for diagnostic challenge for chronic neutropenia—patients suspected to have chronic neutropenia were 'challenged' with doses of G-CSF and observed for elevation in ANC to confirm the diagnosis.[6] Nowadays, the administration of G-CSF has been restricted to short-term treatment in patients with CBN—either for severe infections or before surgical intervention.[4]

Table 1. Chronic benign neutropenia of infancy and childhood in Hong Kong Chinese patients

Patient No.	Sex	Age of onset (months)	Presentation	Type*	Initial ANC† ($x10^9$/L)	Lowest ANC ($x10^9$/L)	Latest ANC ($x10^9$/L)	Outcome‡	Duration of neutropenia (months)	Duration of follow-up (months)
1	F	6	Bilateral vulval abscess	A	0.20	0.10	1.20	PD	25	25
2	M	3	Incidental	A	0.10	0	1.40	PD	27	27
3	M	11	Roseola infantum	A	0	0	1.34	PD	43	43
4	M	6	Lung abscess (sequestrated lung)	C	0.26	0.14	0.50	PD	63	63
5	M	13	Left submandibular abscess	C	0.20	0.20	0.50	PD	21	21
6	M	9	Roseola infantum	C	0.30	0.30	1.27	PD	56	56
7	F	24	Parotitis	C	0.17	0.07	0.10	PD	74	74
8	F	14	Scarlet fever	C	0.44	0.10	0.10	PD	15	15
9	M	9	URTI§	C	0.13	0.06	0.42	PD	26	26
10	F	13	Wheezy bronchitis	C	0.80	0.16	0.66	PD	8	8
11	F	12	Fever and oral ulceration	C	0.08	0	0.88	PD	60	60
12	F	11	Chin abscess with recurrent URTI	C	0.10	0	0.30	PD	29	29
13	M	66	Scarlet fever	C	0.40	0.40	0.50	PD	37	37
14	F	10	Otitis externa	A	0.90	0.06	1.75	SR	25	37
15	F	8	Roseola infantum	C	0.25	0.10	1.80	SR	23	116
16	M	6	Right thigh abscess and pneumonia	C	0.09	0.09	6.15	SR	23	118
17	F	3	Acute gastro-enteritis	C	0.41	0.15	3.87	SR	29	107
18	F	4	Cytomegalovirus infection	C	0.04	0.04	2.20	SR	7	64
19	M	10	Acute gastro-enteritis	C	0	0	7.10	SR	25	49
20	F	2	URTI	C	0.70	0.70	1.70	SR	30	98
21	F	12	Croup	C	0.06	0.06	1.60	SR	8	32
22	M	25	Hand, foot and mouth disease	C	0.49	0.49	3.20	SR	11	91
23	M	1.5	Umbilical sepsis	C	0.33	0.33	2.30	SR	13	72
24	M	8	Roseola infantum	C	0.27	0.27	4.10	SR	9	89

* A: autoimmune neutropenia; C: chronic idiopathic neutropenia
† ANC absolute neutrophil count
‡ PD: persistent disease; SR: spontaneous remission
§ URTI upper respiratory tract infection

Each episode of infection that required hospitalisation was also reviewed. 'Significant' infection was defined arbitrarily as infection requiring hospital admission plus either surgical intervention or intravenous therapy (intravenous antibiotics or intravenous fluid replacement). Remission was defined as persistent normalisation of the neutrophil count (≥1.5 x 10^9 /L) for more than 3 months. The projected remission rate at a certain interval was calculated as the cumulative incidence of recovery. Univariate analysis was used to determine potential factors affecting remission, including the age of onset, presenting features, initial neutrophil count, lowest neutrophil count, bone marrow findings, anti-neutrophil antibody test results, number of hospitalised infections in the first year after diagnosis, and total number of hospitalised infections. Multivariate logistic regression was also performed with these factors as independent variables. A cut-off P value of ≤0.05 was taken as statistically significant.

Results

The median age at presentation was 9.0 months (range, 1.5-66.0 months), and the male-to-female ratio was 1:1. The presenting features are summarised in Table 1. The majority of patients presented with various forms of infection, whereas one patient was discovered incidentally after surgery for ventricular septal defect. No patient had a family history for chronic neutropenia during infancy.

The mean (standard deviation [SD]) ANC on presentation was 0.28 x 10^9 /L (0.24 x 10^9 /L) and the median ANC was 0.23 x 10^9 /L (range, 0-0.49 x 10^9 /L). Of the 19 patients who were tested for anti-neutrophil antibodies, four (21%) had positive results and were classified as having AIN; the majority (15 patients, 79%) were thus classified as having CIN. As associated findings, monocytosis and thrombocytosis were relatively common; they affected 25% and 40% of patients, respectively. Immunoglobulin profiles were obtained for 18 patients and were generally similar to the age- and sex-matched immunoglobulin levels of local Hong Kong Chinese children.[12] Twelve patients had normal profiles, two had an increased level of one immunoglobulin (IgA [n=1]; IgG [n=1]), three had increased levels of two immunoglobulins (both IgA and IgG [n=2]; both IgG and IgM [n=1]), and one patient had increased levels of all three immunoglobulins.

Bone marrow examination had been performed in 17 (71%) patients. Results of nine (53%) patients were normal, whereas six (35%) showed evidence of increased granulopoiesis, which suggested peripheral consumption. One of the two remaining patients showed late-maturation arrest at band stage; the other showed prominent histiocytes

Table 2. Location and frequency of hospitalised infections in 24 patients with chronic benign neutropenia

Location	No. (%)	Occurred in the first year after diagnosis No. (%)	Required intravenous therapy	Required surgical intervention	Pathogens
Childhood exanthema	10 (14)	7 (10)	0	0	4 roseola; 4 chickenpox; 1 hand, foot and mouth disease; 1 scarlet fever
Upper respiratory tract and ear, nose, and throat infections	43 (61)	22 (31)	0	0	3 parainfluenza; 1 adenovirus; others not identified/documented
Lower respiratory tract infection	3 (5)	3 (5)	2 (intravenous antibiotics)	0	2 *Pseudomonas aeruginosa*; others not identified
Gastro-enteritis	4 (6)	2 (3)	1 (intravenous fluid replacement)	0	1 *Escherichia coli*; others not identified
Skin and connective tissue infection and abscesses*	10 (14)	10 (14)	4 (intravenous antibiotics for the 4 surgical cases)	4 (left submandibular abscess, right thigh abscess, bilateral vulval abscess and scalp abscess)	4 cases required surgery (1 *Staphylococcus aureus*, 1 *Pseudomonas aeruginosa*, 1 mixed growth, 1 not identified); 3 cases of methicillin-sensitive *Staphylococcus aureus*; 3 cases not identified
Total	70 (100)	44 (63)	7	4	-

* Granulocyte-colony stimulating factor was used in the patient with thigh abscess, and in two other patients for diagnostic challenge

and phagocytosis of myeloid cells. These findings have all been reported in a previous series[4] and were compatible with the diagnosis of CBN. Marrow examination had not been performed in seven (29%) patients, either because of parental refusal or because the clinician decided to use a 'wait and see' approach.

There were a total of 70 episodes of infection that required hospitalisation (Table 2), corresponding to a rate of 51.6 per 1000 patient-months. More than 70% of these infection episodes were cases of upper respiratory tract infection (URTI) and childhood exanthema. The remaining 17 infection episodes were skin and soft-tissue infections (14%), lower respiratory tract infections (5%), and gastro-enteritis (6%). Of these 17 episodes, nine had pathogens identified and all were bacteria. Of all 70 infection episodes, seven were by definition 'significant' (Table 2) and required either surgery or some form of intravenous therapy. During these significant infections, the mean ANC was 0.20 x 10^9 /L (range, 0.09-0.40 x 10^9 /L). All other cases ran a benign course and did not require treatment beyond symptomatic management or oral antibiotics. Only the four cases of soft-tissue abscess required surgical intervention in the form of incision and drainage. In all, G-CSF was given to only three patients: for diagnostic challenge in two, and to increase the neutrophil count before incision and drainage in the third patient, who had a right thigh abscess complicated by erythema gangrenosum. Although the neutrophil count increased transiently in all three cases, it did not last longer than 7 days. A recurrent chest infection was observed in a patient who had a concomitant sequestrated lung. Recurrence of significant infections was not seen in other patients. Eighty-eight percent of all significant infections and 63% of all hospitalised infections occurred within the first year of diagnosis.

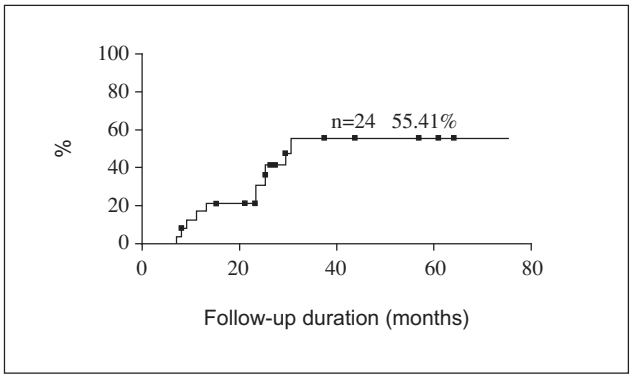

Fig . Probability of achieving remission in chronic benign neutropenia of infancy

During the follow-up period, the mean (SD) of the lowest recorded ANC was 0.16 x 10^9 /L (0.11 x 10^9 /L) and median was 0.10 x 10^9 /L (range, 0-0.49 x 10^9 /L). For 12 (50%) of the patients, the ANC was lowest at presentation, and for 20 (83%), it was within the first year of diagnosis. Thirteen patients had persistent disease until the last follow-up visit, when the mean (SD) ANC was 0.5 x 10^9 /L (0.4 x 10^9 /L) and median was 0.42 x 10^9 /L (range, 0.1-1.34 x 10^9 /L). There was a significant increase in the mean ANC when comparing the lowest value with the ANC value at the last follow-up ($P<0.01$).

Eleven (46%) children eventually achieved remission. The estimated remission rate at 3 years was 55.4% (Fig). After 3 years of follow-up, the rate of remission seemed to reach a plateau, and no new cases of remission were detected. All the remissions were spontaneous and were not related to the use of G-CSF. There was no documented relapse after remission. Univariate analysis and multivariate

logistic regression both showed that the likelihood of remission was not associated with any of the following factors: age of presentation (P=0.423), presence of anti-neutrophil antibody (P=0.577), initial ANC (P=0.611), lowest ANC (P=0.537), normal bone marrow (P=0.27), total number of hospitalised infections (P=0.639), and the number of hospitalised infections in the first year after diagnosis (P=0.706).

Discussion

We report on a cohort of 24 Chinese patients with paediatric CBN during a 10-year period. Although cyclic and congenital neutropenia were excluded conditions, actually no cases were identified from our clinic database. Yet, the cohort in the series of Hong Kong children described by Leung et al[13] was more heterogeneous and consisted of five patients with congenital neutropenia, six with cyclic neutropenia, two with AIN, and five with idiopathic neutropenia. We cannot explain this heterogeneity, because details of the diagnostic criteria cannot be found in their article. Still, among their series, two of the five patients with congenital neutropenia and four of their six patients with cyclic neutropenia had spontaneous remission. The incidence and spectrum of infections were also not described, and thus limited the comparison of the propensity for infection with that in our study.

Patients in western series of Bux et al[4] and Lalezari et al[5] and those in our study shared similar clinical characteristics—namely, the age of onset (9, 8, and 9 months, respectively), male-to-female ratio (1:1, 4.6:5.4, and 4:6, respectively), and associated monocytosis. In our study, increased immunoglobulin level was found in 6 (25%) of the 24 patients. This finding has also been reported previously and was postulated to be due to chronic immune stimulation.[14] No patients in our series had a decreased level of immunoglobulin, which was suggestive of humoral immunodeficiency. The positivity rate for anti-neutrophil antibodies was low in our series. This finding could be partly because repeating anti-neutrophil antibody studies was not a routine practice in our unit in the earlier years of the study period. Patients were not retested, despite testing negative during initial investigations, because a previous study,[1] as well as our own experience, suggested that AIN and CIN were similar in clinical course and prognosis, irrespective of the presence of anti-neutrophil antibody. In our cohort of 24 patients, only one has been tested twice for anti-neutrophil antibody and results on both occasions were negative. Bux et al[4] found it was sometimes necessary to repeat studies up to 3 times before antibodies could be detected.

The hospitalised infection rate in our study was 51.6 events per 1000 patient-months, which corresponded to 0.62 hospitalised events per patient-year. More than 70% of the infections were URTI or childhood exanthema in which no pathogens could be identified. In addition, the hospitalisation rate for URTI was 31.4 per 1000 patient-months among the patients; half of the events occurred in the first year of diagnosis. Local data on the hospitalisation rate for URTI in children was not available, but given the fact that a normal healthy child could have up to eight URTIs per year,[15] these figures might reflect merely the 'background' infections occurring even in the healthy paediatric population. Furthermore, URTIs in children are commonly viral in origin, and their occurrence is probably unrelated to neutropenia, which predisposes to bacterial infection.[16] The relatively high admission rate for URTI in the first year after diagnosis could be explained by the younger age at diagnosis, which made the patients more prone to develop infections. Moreover, the 'cautiousness' of parents having a child who had recently received a diagnosis of CBN no doubt led them to seek medical attention whenever their children developed a fever. On the other hand, six of the seven cases we considered as 'significant' were positive for bacterial culture (two cases of *Pseudomonas* pneumonia, one case of *Escherichia coli* gastro-enteritis, and three cases of soft-tissue and skin abscesses), and it seems that they were more representative of cases related to chronic neutropenia. All seven cases occurred within first year of diagnosis. None of the infections had any major long-term consequences. Recurrent cases had associated risk factors (eg anatomical defects such as sequestrated lung). These findings demonstrated the benign nature of the disease. Furthermore, all patients remained stable after the first year of diagnosis regardless of their ANC and remission status.

The projected remission rate was 55.4% at 3 years, with a mean duration of neutropenia of 28.6 months. The mean duration of disease was 20 months in the cohort of Lalezari et al[5] and 7-25 months in that of Bux et al[4]; more than 90% of patients in these two series displayed spontaneous remission. Patients in our study seem to have a lower remission rate than that reported. This difference could be because of our stringent criteria of remission (ANC of $>1.5 \times 10^9$ /L). If an ANC of at least 1.0×10^9 /L was taken as our remission criteria, there would have been four more cases of remission, giving us a remission rate of 77.8% at 3 years. It would be interesting to follow up the patients with persistent disease to see whether remission could be achieved later. However, even for these patients, the ANC increased from the lowest median value of 0.10×10^9 /L to 0.42×10^9 /L at the most recent follow-up visit. We could not identify prognostic factors in predicting remission in chronic neutropenia of infancy. Similarly, no independent prognostic factors could be identified in the study of Leung et al[13] from multiple logistic regression analysis. Our small sample probably did not have the statistical power to draw any definite conclusion.

In summary, patients with CBN experienced a relatively benign clinical course regardless of their remission status. However, thorough investigation and repeated assessment would be essential to exclude other causes of neutropenia

that have more serious complications—for example, Kostmann syndrome and other forms of congenital neutropenia. A multi-centre prospective study may help identify predictive factors of remission.

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