tory variables hemoglobin type, α+thalassemia genotype, age (in 2 year blocks), sex, fever (> or ≤37.5°C), malaria parasite positivity, C-reactive protein, and status unclassifiable (0,1). We found no evidence for an association between either hemoglobinopathy and protection against iron deficiency: the adjusted ORs for –α/αα and for –α/–α were 1.51 (0.76,3.01; p=0.239) and 0.94 (0.40,2.20; p=0.880), respectively and the OR for HbAS was 1.27 (0.55,2.90; p=0.572). Moreover, while the prevalence of iron deficiency declined with age in completely normal children (αα/αα with HbAA) [OR 0.28 in children <24 months compared to children <24 months of age (0.08,0.94); p=0.039; n=54], it did not decline in either heterozygous [OR 0.47 (0.18,1.23); p=0.124; n=94], or homozygous [OR 1.03 (0.23,4.53); p=0.967; n=37] α+thalassemia. Too few children had the genotype αα/αα and HbAS (n=6) to allow for meaningful interpretation. Although data on biochemical iron markers have been presented for both α+thalassemia and HbAS in several African populations,[8] it is difficult to interpret such data in the absence of information on fever, inflammatory markers, or malaria parasitemia. In the current study we took account of these parameters, and found no evidence that either condition protects against iron deficiency. While it is well established that both HbAS and α+thalassemia are strongly protective against severe *P. falciparum* malaria,[1,9] susceptibility is also affected by a range of other host-related factors. There is some evidence to suggest that iron deficiency may protect against malaria,[10] a hypothesis supported by our recent observations on the coast of Kenya.[6] In this context, the trend we found towards reduced iron status in both conditions is interesting - if this holds up in further studies it could constitute one mechanism by which these conditions result in malaria protection.

Alice M. Nyakeriga,°# Marita Troye-Blomberg,° Jedidah K. Mwacharo,* Sammy Wambua,* Thomas N. Williams*@*

**KEMRI/Wellcome Trust Programme, Centre for Geographic Medicine Research, Coast, Kilifi District Hospital, Kilifi, Kenya; °Stockholm University, Department of Immunology Wenner-Gren Institute, Stockholm, Sweden; #Moi University, Faculty of Health Sciences, Eldoret, Kenya; @Nuffield Department of Clinical Medicine, Oxford OX39DU, UK*

Acknowledgments: we thank Hedvig Perlmann, Roland Erklof, Rune Back, and Brett Lowe for technical support and an anonymous reviewer for helpful suggestions on the presentation of our data.

Funding: this work was supported by UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), the Swedish Agency (Sida/Sarec) for Research Cooperation with developing countries, and the Wellcome Trust, UK. This paper is published with the permission of the Director of KEMRI.

Key words: thalassemia, HbAS, iron status, malaria.

Correspondence: Thomas N. Williams, KEMRI/Wellcome Trust Programme, Centre for Geographic Medicine Research, Coast, PO Box 230, Kilifi, Kenya. Phone: international +254.41.522063. Fax: international +254.41.522390. E-mail: twilliams@kilifi.mimcom.net

References

1. Allen SJ, O'Donnell A, Alexander ND, Alpers MP, Peto TE, Clegg JB, et al. α(+)thalassemia protects children against disease caused by other infections as well as malaria. Proc Natl Acad Sci USA 1997;94:14736-41.
2. Williams TN, Maitland K, Bennett S, Ganczakowski M, Peto TE, Newbold CI, et al. High incidence of malaria in α-thalassaemic children. Nature 1996;383:522-5.
3. Sonakul D, Sook-aneak M, Pacharee P. Pathology of thalassemic diseases in Thailand. J Med Assoc Thai 1978;61:72-4.
4. Pippard MJ, Callender ST, Warner GT, Weatherall DJ. Iron absorption and loading in β-thalassaemia intermedia. Lancet 1979;2:819-21.
5. Rees DC, Williams TN, Maitland K, Clegg JB, Weatherall DJ. α thalassaemia is associated with increased soluble transferrin receptor levels. Br J Haematol 1998;103:365-9.
6. Nyakeriga AM, Troye-Blomberg M, Dorfman JR, Alexander ND, Back R, Kortok M, et al. Iron deficiency and malaria among children living on the coast of Kenya. J Infect Dis 2004; 190:439-47.
7. Chong SS, Boehm CD, Higgs DR, Cutting GR. Single-tube multiplex-PCR screen for common deletional determinants of α-thalassemia. Blood 2000;95:360-2.
8. Mockenhaupt FP, Bienzle U, May J, Falusi AG, Ademowo OG, Olumese PE, et al. Plasmodium falciparum infection: influence on hemoglobin levels in α-thalassemia and microcytosis. J Infect Dis 1999;180:925-8.
9. Hill AV, Allsopp CE, Kwiatkowski D, Anstey NM, Twumasi P, Rowe PA, et al. Common west African HLA antigens are associated with protection from severe malaria. Nature 1991; 352:595-600.
10. Oppenheimer SJ. Iron and its relation to immunity and infectious disease. J Nutr 2001;131:616S-33S.

Immunodeficiency Syndromes

Neutropenia in Iranian patients with primary immunodeficiency disorders

Neutropenia may occur in some of the primary immunodeficiency disorders. We reviewed the records of 56 neutropenic patients. The most common disorders were Shwachman-Diamond syndrome, cyclic neutropenia, Kostmann disease, Chediak-Higashi syndrome, hyper IgM syndromes, severe combined immunodeficiency, hyper IgE syndrome, and common variable immunodeficiency.

haematologica 2005; 90:554-556
(*http://www.haematologica.org/journal/2005/4/554.html*)

Primary immunodeficiency disorders (PiD) are relatively rare disorders, characterized by an unusual susceptibility to infections.[1,2] Some conditions with PiD may also feature neutropenia as a consequence of either an intercurrent infection or an autoimmune disease.[3,4] The present study reports the clinical and laboratory findings of Iranian PiD patients with associated neutropenia from a main immunodeficiency referral center in Iran.

Four hundred and seventy-four patients with the diagnosis of PiD have so far been referred to the Iranian Primary Immunodeficiency Registry (IPIDR) during a 24-year period (1980-2004).[2] A review of the clinical records of all these patients identified 56 (11.8%) with associated neutropenia. These patients' data were collected by interview and review of their medical documents.

The characteristics of the 56 cases (32 males, 24 females) with associated neutropenia are shown in Table 1. The mean age of these patients with neutropenia was 10.7±5.7 years (range: 2-25 years), and they were followed through a period of 7.9±4.6 years. The median age at the onset of the PiD disorder was 6.5 months (1-134). The median age at the time of PiD diagnosis was 3 years (2 months-13 years), with a median diagnosis delay of 23 months (<1 month - 12 years). Thirty-nine out of these patients are alive, 10 patients could not be located since one year previously, and the remaining 7 patients have

Table 1A. Frequency of neutropenia in primary immunodeficiency disorders.

Name of disease	Registered patients (n=474)		Patients with neutropenia (n=56)		Incidence of neutropenia
	Number	Percent	Number	Percent	
Deficiencies predominantly affecting antibody production					
X-linked agammaglobulinemia	45	9.49	3	5.36	6.67%
Common variable immunodeficiency	109	22.99	13	23.21	11.93%
Selective IgA deficiency	35	7.38	0	0	0%
IgG subclass deficiency	10	2.11	0	0	0%
Combined B- and T-cell deficiencies					
Severe combined immunodeficiency	19	4.01	3	5.36	15.79%
Hyper IgM syndromes	8	1.69	3	5.36	37.5%

Table 1B. Frequency of neutropenia in primary immunodeficiency disorders.

Name of disease	Registered patients (n=474)		Patients with neutropenia (n=56)		Incidence of neutropenia
	Number	Percent	Number	Percent	
Other well-defined immunodeficiency syndromes					
Wiskott-Aldrich syndr.	8	1.69	0	0	0%
DiGeorge anomaly	1	0.21	0	0	0%
Hyper IgE syndrome	15	3.16	2	3.57	13.33%
Chronic mucocutaneous candidiasis	12	2.53	1	1.79	8.33%
Ataxia - telangiectasia	75	15.82	3	5.36	4%
Defects of phagocyte function					
Chronic granulomatous disease	81	17.09	2	3.57	2.47%
Leukocyte adhesion defects	17	3.59	1	1.79	5.88%
Chediak-Higashi syndrome	10	2.11	5	8.93	50.00%
Myeloperoxidase deficiency	2	0.42	0	0	0%
Cyclic neutropenia	7	1.48	7	12.5	100%
Kostmann disease	6	1.27	6	10.71	100%
Shwachman-Diamond syndrome	7	1.48	7	12.5	100%
Defects of the complement proteins					
C1 inhibitor deficiency	5	1.05	0	0	0%
C2, C4 deficiency	2	0.42	0	0	0%

died because of recurrent infections. Laboratory analysis revealed that the absolute neutrophil count was low in these patients, with the mean count being 0.666± 0.423×10⁹/L (range: 0.025-0.1376×10⁹/L) at the time of diagnosis. The median counts of white blood cells and monocytes were: 3.635×10⁹/L (range: 1.62-9.6×10⁹/L) and 0.204×10⁹/L (range: 0.024-1.48×10⁹/L), respectively.

Table 2. Laboratory findings of neutropenic patients according to type of primary immunodeficiency disorder.

Primary immunodeficiency disorder	Absolute neutrophil count	Severity of neutropenia			Pattern of neutropenia			
	Median (range)	Severe	Moderate	Mild	Transient	Recurrent	Chronic	Leukopenia
X-linked agammaglobulinemia	1368 (696-1368)	–	1	2	3	–	–	1
Common variable immunodeficiency	910 (25-1324)	5	5	3	7	2	4	1
Severe combined immunodeficiency	567 (288-1376)	1	1	1	–	–	3	9
Hyper IgM syndromes	768 (200-864)	1	2	–	1	–	2	2
Hyper IgE syndrome	860 (384-1336)	1	–	1	2	–	–	–
Chronic mucocutaneous candidiasis	1176	–	–	1	1	–	–	–
Ataxia - telangiectasia	1080 (776-1353)	–	1	2	3	-	–	3
Chronic granulomatous disease	1183 (1080-1286)	–	–	2	2	–	–	1
Leukocyte adhesion defects	195	1	–	–	–	–	1	–
Chediak-Higashi syndrome	551 (312-1152)	2	2	1	–	–	5	4
Cyclic neutropenia	250 (74-900)	6	1	–	–	7	–	3
Kostmann disease	333 (188-625)	4	2	–	–	–	6	2
Shwachman-Diamond syndrome	435 (213-1200)	5	1	1	–	2	5	6

According to the classification of neutropenia, 26 patients suffered from severe, 16 moderate, and 14 from mild neutropenia. Single episodes of transient neutropenia have been seen in 19 patients. Twenty-six had experienced chronic neutropenia and 11 cases had recurrent neutropenia (Table 2). Also, 32 out of these patients showed leukopenia (57.1%), 24 had anemia (42.9%), 11 thrombocytopenia, and only 3 patients had monocytosis. The most common infections during the course of the illness were respiratory infections, which were seen in 48 patients (85.7%). Other manifestations were: pneumonia (30 cases), otitis media (28 cases), acute diarrhea (28 cases), abscess (24 cases), oral candidiasis (23 cases), oral ulcers (17 cases), cutaneous infections (16 cases), and sinusitis (12 cases). Other less frequent infections were: periodontitis or conjunctivitis (5 cases), cystitis (2 cases), meningitis (2 cases), and osteomyelitis (1 case). Abscesses were detected in different sites, including: perianal (8 cases), cutaneous (7 cases), submandibular (4 cases), mastoidal (3 cases), dental (3 cases), liver (2 cases), peritonsillar (2 cases), lung (1 case), and soft tissue (1 case). The non-specific signs of hepatomegaly and splenomegaly had already been found in 41.1% and 32.1% of the patients, respectively. All of the patients with single episodes of neutropenia had had infectious complications during the neutropenic episode, including: pneumonia (5 cases), otitis media (4 cases), diarrhea (2 cases), oral ulcers (2 cases), cutaneous infections (2 cases), abscess (2 cases), sinusitis (1 case), and oral candidiasis (1 case).

Neutropenia may occur in any PiD as a consequence of either an intercurrent infection or an autoimmune disease.[3,4] All of our patients with Shwachman-Diamond syndrome, cyclic neutropenia and Kostmann disease had associated neutropenia. In addition, a number of our patients with predominant antibody deficiency disorders had associated neutropenia. It seems that autoimmune neutropenia is a common cause of neutropenia in some primary specific immunodeficiencies.[3,5,6] An increased susceptibility to infections was detected in our patients. For patients presenting with unexpected neutropenia, the clinical history and examination of the peripheral blood smear were the most important parts of the diagnostic evaluation. Examination of the oral cavity, perianal region, and skin is necessary in order to assess the clinical impact of chronic neutropenia. The presence of gingivitis, ulcer, and abscess implies clinically significant neutropenia.[7,8] Persistent or severe infections should always raise a suspicion, which deserves further evaluation, of an underlying immune deficiency syndrome and neutropenia, because a delay in diagnosis may result in a serious organ damage or even death of the patient.[6,9]

Nima Rezaei, Abolhassan Farhoudi, Zahra Pourpak, Asghar Aghamohammadi, Mostafa Moin, Masoud Movahedi, Mohammad Gharagozlou

Department of Allergy and Clinical Immunology of Children's Medical Center, Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran

Acknowledgements: we are grateful to Drs. Ahmadi-Afshar, Atarod, Bazargan, Chavoshzadeh, Haydarzadeh, Mahmoudi, MirSaeid-Ghazi, Nabavi, and Bemanian who assisted us at every step of this project.

Key words: neutropenia, immunologic deficiency syndromes, infection, Iran.

Correspondence: Zahra Pourpak, MD, PhD, Immunology, Asthma and Allergy Research Institute, Children's Medical Center, No. 62, Dr. Gharib St., Keshavarz Blvd., Tehran 14194, Iran, P.O.Box: 14185-863. Phone: international +98.21.6935855. Fax: international +98.21.6428995. E-mail: rezaei_nima@hbi.ir/ zpourpak@hbi.ir

References

1. Primary immunodeficiency diseases. Report of an IUIS Scientific Committee. International Union of Immunological Societies. Clin Exp Immunol 1999;118 Suppl 1:1-28.
2. Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K, et al. Primary immunodeficiency in Iran: first report of the National Registry of PID in Children and Adults. J Clin Immunol 2002;22:375-80.
3. Cham B, Bonilla MA, Winkelstein J. Neutropenia associated with primary immunodeficiency syndromes. Semin Hematol 2002;39:107-12.
4. Ming JE, Stiehm ER, Graham JM Jr. Syndromic immunodeficiencies: genetic syndromes associated with immune abnormalities. Crit Rev Clin Lab Sci 2003;40:587-642.
5. Lakshman R, Finn A. Neutrophil disorders and their management. J Clin Pathol 2001;54:7-13.
6. Unsworth DJ, Thomas HM. Missed clues and delayed diagnosis of immunodeficiency. Lancet 1997;349:435.
7. Constantinou CL. Differential diagnosis of neutropenia. In: Tefferi A, ed. Primary Hematology. Human Press; Totowa: New Jersey. 2001. p 93-105.
8. Watts RG. Neutropenia. In: Lee GR, Foerster J, Lukens J, Paraskevas F, Greer JP, Rodgers GM, editors. Wintrobe's Clinical Hematology. Lippincott Williams and Wilkins, USA, 1999. p 1862-88.
9. Chapel HM. Consensus on diagnosis and management of primary antibody deficiencies. Br Med J 1994;308:581-5.

Chronic Myeloid Leukemia

Clonal cytogenetic abnormalities in patients with chronic myeloid leukemia in complete cytogenetic response to imatinib mesylate

The emergence of clonal chromosomal abnormalities in Philadelphia-negative cells during treatment with imatinib in patients with Philadelphia-positive chronic myeloid leukemia has been reported. We add information to this issue presenting a series of 29 patients in complete cytogenetic response after imatinib treatment, three of whom developed clonal aberrations.

haematologica 2005; 90:556-558
(*http://www.haematologica.org/journal/2005/4/556.html*)

Chronic myeloid leukemia (CML) is a chronic myeloproliferative disorder (CMPD) characterized by the t(9;22)(q34.1;q11.2) that juxtaposes the *ABL* and *BCR* genes with generation of the Philadelphia chromosome (Ph').[1] The molecular consequence is the *BCR-ABL* oncogene, that encodes a BCR-ABL oncoprotein ($p210^{BCR/ABL}$) with increased tyrosine kinase activity which is necessary and sufficient for leukemogenesis.[2] Imatinib mesylate (STI571, Glivec®, Novartis Pharma, Switzerland), a tyrosine kinase inhibitor selective for ABL, BCR-ABL, c-KIT, PDGFRα and ARG proteins has demonstrated good results in CML. As first line therapy, imatinib is superior to interferon (IFN)-α, inducing complete hematologic responses in 95% of patients, major cytogenetic responses in 85% and complete cytogenetic responses (CCR) in 73%.[3] Imatinib has been proven to be better tolerated, although long-term side effects and influence on long-term survival are not yet known. Recently, some cases of clonal cytogenetic abnormalities in Ph' negative cells of patients with CML treated with imatinib have been