

Changes in the Epidemiology of Thalassemia in North America: A New Minority Disease

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ABSTRACT. *Objective.* Changing patterns of immigration to North America, along with improved treatment, have altered the clinical spectrum of thalassemia, one of the world's most common genetic diseases. The new demography of the disease, with its widely variable phenotypes, has implications for its diagnosis, counseling, and management. Characterization of the new spectrum of this ancient disease, now predominated by minority groups, is essential for optimizing survival.

Methods. The National Institutes of Health–sponsored North American Thalassemia Clinical Research Network (TCRN) conducted a cross-sectional study of 721 patients with thalassemia syndromes. A detailed chart review was undertaken to define the relationships between ethnic origins, genotype, and phenotype. These results were compared with 3 previous surveys of similar regions. To determine if the TCRN patient epidemiology is representative of North American patients, 87 additional programs were reviewed, and hemoglobinopathy programs from the 2 largest thalassemia regions, Ontario and California, were analyzed.

Results. A total of 721 patients completed analysis in the TCRN study, including 389 (54%) patients with β -thalassemia major, 105 (15%) patients with β -thalassemia intermedia, 95 (13%) patients with hemoglobin E- β -thalassemia, and 132 (18%) patients with α -thalassemia. β -Thalassemia predominated in Eastern North America. Hemoglobin E- β -thalassemia and α -thalassemia were common on the Western continent. Genotype broadly correlated with the clinical phenotype. However, there was marked heterogeneity in clinical phenotype among patients with similar globin mutations. In β -thalassemia disorders, coinheritance of the α -thalassemia trait, triplication of α -thalassemia genes, and heterozygosity for the dominant β -thalassemia allele affected the clinical phenotype. In α -thalassemia disorders, structural mutations such as hemoglobin H-Constant Spring resulted in a severe hemoglobin H phenotype. Sixty percent of patients received regular transfusions, and 86% received regular iron-chelation therapy. Increased survival and

decreasing birth rates of Mediterranean patients resulted in an aging Greek/Italian population being replaced by a young Asian/Middle Eastern population. Now, Asian patients account for >50% of the thalassemia population. Evidence of increasing survival is reflected in an advancing mean age of white patients with thalassemia major (25 years, up from 11 years in 1974). The results of the non-TCRN thalassemia survey confirm these observations and describe a young multiethnic thalassemia population distributed throughout North America. Newborn-screening results suggest that thalassemia births in North America are increasing and reflect the change in genotype and phenotype observed in the TCRN populations.

Conclusions. The epidemiology of thalassemia in North America reflects a heterogeneous group of diseases with new ethnicities, genotypes, and phenotypes. In these communities, physicians will need to provide education, prenatal diagnosis, counseling, and management of this newly diverse group of patients. *Pediatrics* 2005;116:e818–e825. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0843; *epidemiology, thalassemia, survival, demography, minority disease, genotype, phenotype.*

ABBREVIATIONS. TCRN, Thalassemia Clinical Research Network; IVS, intervening sequence.

Severe thalassemia, based on observations of Italian children with characteristic anemia and bone deformities, was first described in North America in 1925¹ and later termed “thalassa anemia” (“anemia by the sea”) because of recognized links to the Mediterranean region.² Documented in all ethnic groups originating from geographic regions in which malaria was or remains endemic, thalassemia is an increasing public health problem worldwide.³ Ninety-five percent of affected births occur in Asian, Indian, and Middle Eastern regions, areas from which over the past decade many immigrants have relocated to North America.⁴ Fatal in the absence of modern medical care, thalassemia is associated with extended survival with adherence to transfusion and effective iron-chelation regimens. A high mortality rate has been reported by some authors⁵ but has not been corroborated in expert centers.^{6–9} Although previous reports^{6,7} have focused on smaller cohorts of patients with thalassemia on this continent, neither the demography nor the natural history of the North American population over the last 10 years has been reported. Many genotypes previously considered to be uncommon in North America³ are diagnosed increasingly in many screening programs because of

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Accepted for publication Jun 7, 2005.

doi:10.1542/peds.2005-0843

No conflict of interest declared.

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dramatic population shifts of affected populations to North America. Understanding the phenotypic expression of these syndromes, many of which are not well characterized even in their countries of origin,¹⁰ will be essential for optimizing treatment for North American patients in the new millennium.

The Thalassemia Clinical Research Network (TCRN) of the National Heart, Lung, and Blood Institute examined the demography and natural history of all patients with thalassemia who are registered in the 5 largest treatment centers in North America. The goal of the TCRN is to provide information on the changing face of this disease and the implications for diagnosis, counseling, and treatment.

METHODS

To define the disease spectrum and facilitate clinical research, the TCRN developed a cross-sectional registry to characterize the demographic and clinical features of North American patients. Institutional review boards at all sites and the TCRN Data and Safety Monitoring Board approved the study. Data were included from all living patients who gave informed consent and were diagnosed with α -thalassemia, hemoglobin E- β -thalassemia, β -thalassemia major, or β -thalassemia intermedia, obtained by using a medical-record review supplemented by patient interview. Sickle cell β -thalassemia disorders were excluded from analysis, because it is commonly classified as a sickle cell disease because of its pathophysiology. Demographics, molecular diagnosis, and medical history, focusing on previous and present treatment and complications, were obtained by using a 14-part case-report form. Data were collected once for each subject from June 2001 to January 2004. Ages were determined at enrollment and at the time of specific events. Eighty percent of all forms were reviewed at the individual sites. Independent source-document verification was conducted for selected variables on 30% of the forms.

Age trends in prevalence were tested by Cochran-Armitage trend tests. Associations of categorical variables were tested by Fischer's exact test. Confidence intervals on odds ratios are exact. Analyses were conducted in SAS 8.2 (SAS Institute, Inc, Cary, NC).

Molecular and Clinical Definitions

Diagnosis was based on clinical history and laboratory confirmation by hemoglobin electrophoresis and/or DNA testing. By using common testing panels and following published methods,¹¹ α - and β -globin mutations were determined at reference laboratories. Differentiation of β -thalassemia major and intermedia was based on transfusion requirements over 12 months before entry in the registry: patients receiving ≥ 8 transfusions over that period were classified as thalassemia major; those receiving transfusions on < 8 occasions were termed thalassemia intermedia. All patients with E- β -thalassemia were included in 1 category regardless of transfusion history. Severe α -thalassemia included 1 of 3 genotypes: homozygous α -thalassemia (4 genes deleted), hemoglobin H disease (3 genes deleted), or hemoglobin H-Constant Spring or another nondeletional α -thalassemia allele (with 2 genes deleted on the allele in trans).

Two comparative surveys were completed. The first survey compared the thalassemia population over time within the TCRN regions, and the second survey compared TCRN patient data to patients identified in non-TCRN clinical programs in North America.

In 1973, 1985, and 1993, surveys of patients with thalassemia within the TCRN regions were undertaken.¹²⁻¹⁴ A questionnaire requested listing of all current patients with β -thalassemia major and β -thalassemia intermedia. Respondents were asked not to report patients with α -thalassemia syndromes and double heterozygotes (eg, hemoglobin S- β -thalassemia and hemoglobin E- β -thalassemia). Each patient's date of birth and ethnicity were obtained. The 1973 and 1985 surveys consisted of TCRN center regions Canada, New York State, Northeast (Boston, MA), Philadelphia, PA/Washington, DC, and Chicago, IL.^{12,13} With the ad-

dition of the California region in 1993, $> 90\%$ of the patients surveyed were within the present TCRN center regions. In the 1993 survey, the geographic locations of the 443 patients identified were Canada (116), New York (142), California (52), Northeast (44), Philadelphia (30), Chicago (15), and other (44).¹⁴

To determine if the TCRN patient epidemiology is representative of North American patients, a survey of 87 additional clinical programs representing each region in North America was undertaken. Seventy-two programs actively follow patients with thalassemia (11 do not follow patients, 4 had no response). A questionnaire, with verbal confirmation, collected the number, ethnicity, and age category of patients seen in the last year. The questionnaire included patients with β -thalassemia major and β -thalassemia intermedia according to the definitions given above; respondents were asked not to report patients with α -thalassemia syndromes and double heterozygotes (eg, hemoglobin S- β -thalassemia and hemoglobin E- β -thalassemia).

The number, ethnicity, and genotype of patients with thalassemia detected in hemoglobinopathy programs from the 2 largest thalassemia regions are reported from each reference hemoglobin laboratory. In California, Children's Hospital Oakland Reference Hemoglobin Laboratory and Genetic Disease Branch, California Department of Health Services (F.L.), determined diagnoses in pilot (1975-1985) and statewide (1990 to present) universal newborn-screening programs. In the Province of Ontario (Canada), thalassemia cases were reported through the provincial reference laboratory at McMaster University Medical Centre (1989 to present).

RESULTS

Seven hundred twenty-one enrolled patients completed collection of the registry data: 389 patients with β -thalassemia major, 105 patients with β -thalassemia intermedia, 95 patients with E- β -thalassemia, and 132 patients with α -thalassemia (hemoglobin H [80], hemoglobin H-Constant Spring or another nondeletional mutation [43], and homozygous α -thalassemia [9]). In 519 patients (72%), molecular diagnosis was confirmed by DNA testing. The most prevalent phenotypes are shown in Table 1. Genotype distributions are summarized in Table 2. Note that Tables 1 and 2 report 519 patients who have undergone genotyping, as appropriate for their clinical diagnosis, of either α - or β -globin genes. Therefore, these 519 patients represent patients who have undergone complete α - and β -globin genotyping ($n = 445$) and either α genotyping (but not β -globin genotyping) or β genotyping (but not α -globin genotyping).

Combinations of the alleles shown resulted in 160 genotypes, 134 of which were expressed as β -thalassemia, among 445 patients who had undergone complete genotyping of both α - and β -globin genes. In almost half (44%) of the patients, combinations of 6 common mutations (3 Mediterranean mutations, intervening sequence [IVS] I-110 G \rightarrow A, codon 39 C \rightarrow T, and IVS I-6 T \rightarrow C; and 3 Asian mutations, IVS-I-5 G \rightarrow C, codon 41/42 -TCTT, and -28 A \rightarrow G) resulted in 7 common β -globin genotypes. Eighty-eight percent of the patients with E- β -thalassemia were heterozygous for 1 of 6 Asian/Indian mutations (codon 15 TGG \rightarrow TAG, codon 41/42 -TCTT, codon 17 A \rightarrow T, IVS I-1 G \rightarrow T, IVS I-5 G \rightarrow C, and IVS II-654 C \rightarrow T). Eight percent of E- β -thalassemia syndromes coinherited at least 1 α gene mutation (-^{SEA} (Southeast Asian); -^{FIL} (Filipino); α^{CS} (Constant Spring); $\alpha^{3,7}$; - $\alpha^{4,2}$). These 5 mutations were responsible for 90% of the α -thalassemia genotypes. The hemoglobin H-Constant Spring mutation was present in 27% of the patients with α -thalassemia.

TABLE 1. β and α Mutations Associated With Each Thalassemia Phenotype

Phenotype	<i>n</i>
Thalassemia major	275
Codon 39 (C→T) β^0 /IVS I-110 (G→A) β^+	30
IVS I-110 (G→A) β^+ /IVS I-110 (G→A) β^+	28
Codon 39 (C→T) β^0 /codon 39 (C→T) β^0	16
IVS I-5 (G→C) β^+ /IVS I-5 (G→C) β^+	14
Codon 39 (C→T) β^0 /IVS I-6 (T→C) β^+	12
IVS I-6 (T→C) β^+ /IVS I-110 (G→A) β^+	11
-28 (A→G) β^+ /codon 41/42 (-TCTT) β^0	10
Other genotypes	154
Thalassemia intermedia	78
IVS I-6 (T→C) β^+ /IVS I-6 (T→C) β^+	5
Hb A/codon 39 (C→T) β^0	4
Codon 41/42 (-TCTT) β^0 /codon 41/42 (-TCTT) β^0	4
-28 (A→G) β^+ /-28 (A→G) β^+	3
Codon 39 (C→T) β^0 /IVS I-6 (T→C) β^+	3
IVS I-5 (G→C) β^+ /IVS I-5 (G→C) β^+	3
Codon 8/9 (+G) β^0 /IVS II-1 (G→A) β^0	2
Other genotypes	54
α -Thalassemia	109
SEA deletion/3.7-kb deletion	37
SEA deletion/Constant Spring	29
Filipino deletion/3.7-kb deletion	13
SEA deletion/4.2-kb deletion	9
SEA deletion/SEA deletion	9
20.5-kb deletion/3.7-kb deletion	2
SEA deletion/Hb Dartmouth	2
Other genotypes	8
E- β -Thalassemia	57
Hb E/codon 41/42 (-TCTT) β^0	21
Hb E/codon 17 (A→T) β^0	16
Hb E/IVS I-5 (G→C) β^+	5
Hb E/IVS I-1 (G→T) β^0	3
Hb E/IVS II-654 (C→T) β^+	3
Hb E/codon 39 (C→T) β^0	2
Hb E/codon 15 (G→A) β^0	2
Hb E/other genotypes	5

n indicates the number of patients with complete DNA genotype results; SEA, Southeast Asian; kb, kilobases; Hb, hemoglobin; →, base pair change.

Genotype was broadly correlated with phenotype: 87% of patients with a homozygous β^0 thalassemia genotype were clinically thalassemia major phenotypes (Table 2). Coinheritance of the α -thalassemia trait was weakly associated with reduced transfusion requirement in β^0/β^0 patients (33% of patients with thalassemia intermedia with this genotype, compared with 11% of patients who received regular transfusions, have the α -thalassemia trait; $P = .10$). A severe thalassemia phenotype associated with a single β -thalassemia mutation (in which only 1 abnormal β allele was identified) was detected in 15 patients (13 with thalassemia intermedia, 2 with thalassemia major). These phenotypes were associated with the triplication and quadruplication of α genes, or heterozygosity for a dominant β -thalassemia allele.¹⁵ The transfusion status of patients with E- β^0 -thalassemia did not seem to be affected by the coinheritance of α mutations. Hemoglobin H-Constant Spring disorders were more likely, compared with those with hemoglobin H disease resulting from gene deletions, to require regular transfusions (33% vs 0%; $P < .001$) and to have undergone splenectomy (17% vs 0%; $P < .01$).

Analysis of the geographic distribution showed 228 patients in the Toronto region, 214 in California,

138 in New York City, 65 in Philadelphia/Washington, DC, 38 in Chicago, and 36 in Northeast (Boston, MA). Diagnoses of thalassemia major and intermedia predominate in the eastern parts of the continent, whereas α -thalassemia and E- β -thalassemia are more common in the western regions.

The ethnic background of patients by diagnosis included 43% white, 51% Asian, and 6% black or multiethnic (Table 3). There is a strong association between ethnicity and patient genotype; nearly all white patients have β -thalassemia major and intermedia, whereas individuals of nonwhite descent account for nearly 40% of patients with β -thalassemia major and intermedia. Of the patients with hemoglobin H and E- β -thalassemia, 80% and 90%, respectively, are Asian.

Figure 1 shows the relationship between ethnicity and age in the current population. Three quarters of the infants and children are of Asian and Middle Eastern origins. By contrast, two thirds of the surviving adults are white. These differences are amplified when specific genotypes are analyzed. α -Thalassemia and E- β -thalassemia are predominantly pediatric Asian disorders. Pediatric patients with thalassemia major and intermedia are predominantly Middle Eastern and Asian, whereas affected adults are white.

Since 1973, 4 of the 5 thalassemia TCRN regions have been jointly collecting data about the demography of thalassemia; California was added in 1983. Data comparing thalassemia epidemiology over time from these regions are analyzed in Figs. 2 and 3. Increased survival and decreasing birth rates of Mediterranean patients result in an aging Greek/Italian population being replaced by a young Asian/Middle Eastern population.

Figure 2 examines the age distribution of thalassemia major patients over several decades. The differences between the mean ages reported in 1973, 1985, 1993, and 2003 are all significant, with the largest increase observed in the most recent decade. The percentage of patients living past 25 years also increased dramatically over the last 3 decades. In 1973, 2% of the population exceeded the age of 25 years, increasing to 7% in 1985.^{13,14} At the time of this writing, 36% of the patients were older than 25 years. From 1973 through 1993, there were 4 patients with thalassemia major who were 40 to 50 years old. In this analysis, 17 (4%) patients were older than 40 years, and 2 (0.5%) were 51 years old.

Figure 3 compares the ages and ethnicity of patients with thalassemia major within the TCRN regions. Italian/Greek patients are compared with others over the last decade. Newborns and children are predominately non-Mediterranean; older adult patients seem to be surviving longer and are largely Mediterranean.

Recent immigration changes and subsequent thalassemia birth rates are most likely responsible for the high proportion of Asian children with thalassemia. These changes are not reflected yet in the adult thalassemia population. In the last 3 decades, census data indicate a 2000% increase in Asian immigration preceded by a corresponding decrease in Mediterra-

TABLE 2. Genotypes of Patients With Thalassemia in North America According to Disease Type

	Thalassemia Major (n = 275), n (%)	Thalassemia Intermedia (n = 78), n (%)	α -Thalassemia (n = 109), n (%)	E- β -Thalassemia (n = 57), n (%)
β^0/β^0	77 (28)	12 (15)		
β^0/β^+	110 (40)	19 (24)		
β^+/β^+	86 (31)	34 (44)		
A/ β^0	2 (1)	12 (15)		
A/ β^+		1 (1)		
E/ β^0				49 (86)
E/ β^+				8 (14)
-/-			9 (8)	
-/- α			64 (59)	
-/(T) α			36 (33)	

See text for comodifiers of the above genotype: α -thalassemia, α -triplication, α -quadruplication, and heterozygosity for dominant β -thalassemia allele. *n* indicates the number of patients with complete DNA genotype results; A, normal β -globin gene; A/ β^0 , dominant heterozygote for β^0 ; A/ β^+ , dominant heterozygote for β^+ ; -/-, 4 α gene deletions; -/ α (T) α , α gene deletions with structural mutation (eg, H-Constant Spring).

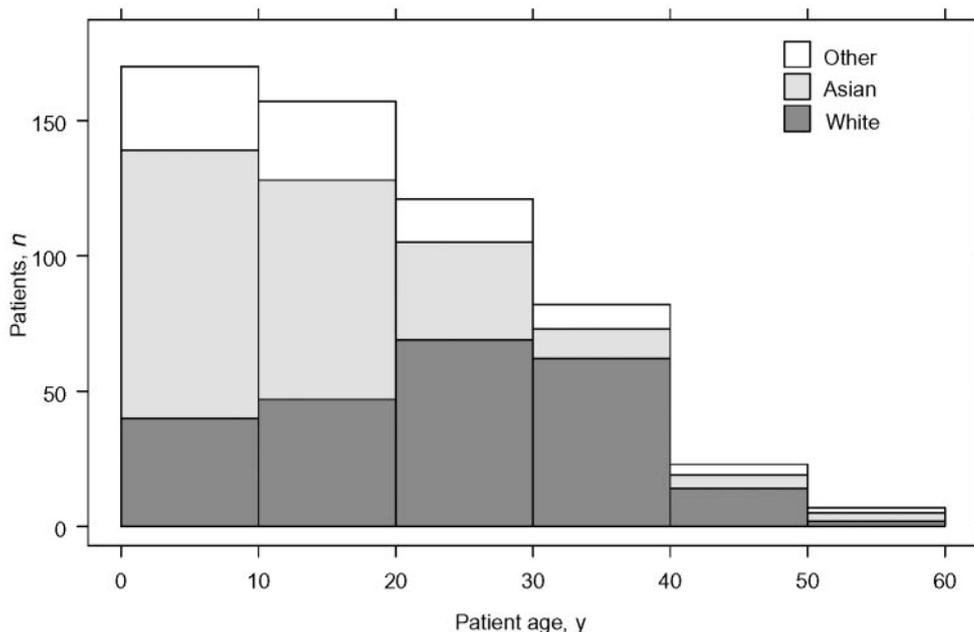
TABLE 3. Ethnicity of Patients With Thalassemia in North America According to Disease Type

	Total, n (%)	Thalassemia Major, n (%)	Thalassemia Intermedia, n (%)	α -Thalassemia, n (%)	E- β -Thalassemia, n (%)
White	312 (43)	240 (62)	65 (62)	5 (4)	2 (2)
Greek/Italian	216 (30)	182 (47)	32 (30)	2 (2)	0 (0)
Other white*	96 (13)	58 (15)	33 (31)	3 (2)	2 (2)
Asian	368 (51)	136 (35)	28 (27)	112 (85)	92 (97)
Indian/Pakistani	82 (11)	59 (15)	11 (10)	4 (3)	8 (8)
Chinese	95 (13)	50 (13)	9 (9)	26 (20)	10 (11)
Southeast Asian	147 (20)	10 (3)	5 (5)	70 (53)	62 (65)
Other Asian†	44 (6)	17 (4)	3 (3)	12 (9)	12 (13)
Other ethnicities‡	41 (6)	13 (3)	12 (11)	15 (11)	1 (1)
Total	721	389	105	132	95

* "Other white" includes other European, North African, Middle Eastern, and Hispanic.

† "Other Asian" includes mixed Chinese, Southeast Asian, and Afghani.

‡ "Other" ethnicities include African, black, mixed ethnic, and unknown.

**Fig 1.** Ethnicity and age of patients with thalassemia (includes all 721 patients with thalassemia).

nean immigration (Fig. 4).¹⁶ This change in immigration is reflected by similar trends in thalassemia births. Hemoglobinopathy programs from California and Ontario, which account for the majority of TCRN patients, illustrate the increasing number and chang-

ing ethnicity and genotype of thalassemia births (Fig. 5; Table 4). 1975 to 1989 refers to pilot newborn screening, making rate comparisons with the 1990-to-present interval difficult. In the 1970s, 70% (7 of 10) of newborns with β -thalassemia major in Califor-

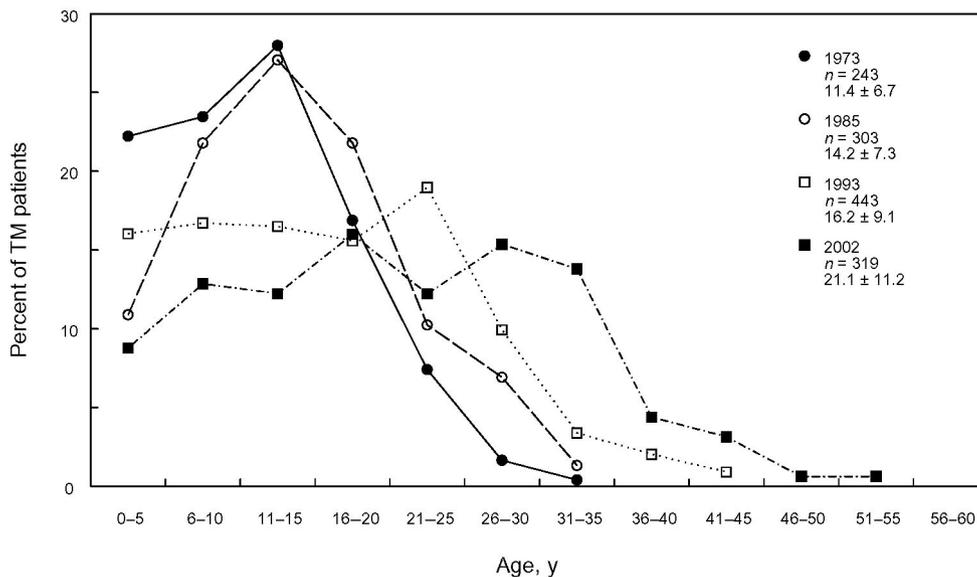


Fig 2. Age distribution of patients with thalassemia major (TM): the age distribution of patients with thalassemia major in the present TCRN North American study (2003) are compared with 3 previous thalassemia major surveys (1973, 1985, and 1993) of similar regions.¹²⁻¹⁴

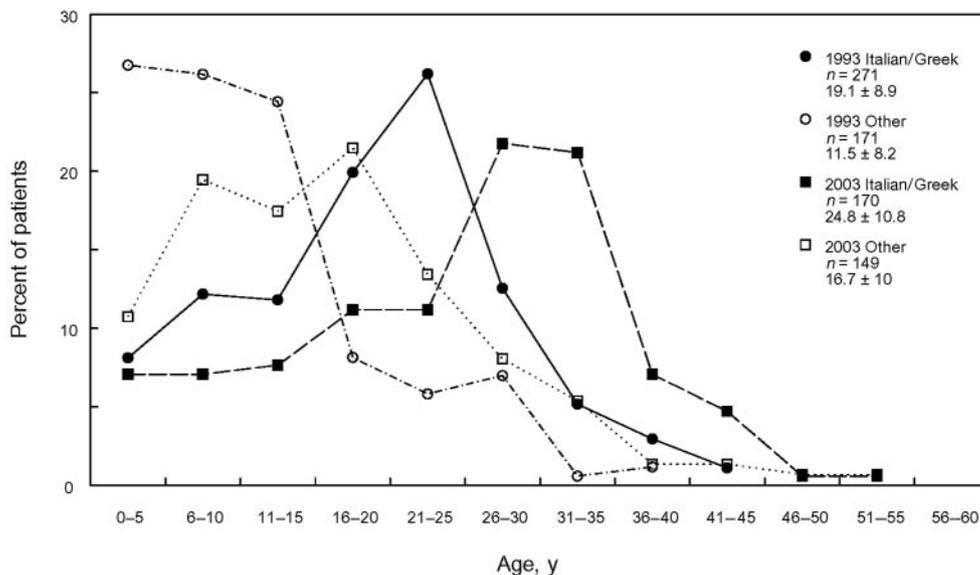


Fig 3. Age distribution of Italian/Greek patients with thalassemia major versus others: the ethnicity and age distribution of patients with thalassemia major in the present TCRN North American study (2003) are compared with a previous thalassemia major survey of the same programs (1993).¹⁴

nia were white, in contrast to 16% (9 of 56) of the patients in the last decade. A similar trend is evident for Ontario, in which 65% (36 of 55) of the patients with β -thalassemia born in the 1970s were of Southern European descent, compared with 21% (15 of 71) born after 1990. Of the 39 patients with β -thalassemia identified in the 1960s, 59% were southern European. In the last decade, 21% of the 71 identified patients were southern European.

The results of the North American non-TCRN thalassemia survey indicate a young, multiethnic population limited in the number of patients within each program and widely dispersed throughout all regions. Eighty-three percent (72 of 87) of programs surveyed followed patients with β -thalassemia. The

results included 355 patients (231 with thalassemia major, 118 with thalassemia intermedia, and 6 unclassified). Thirty-five states had patients with thalassemia representing all regions (32% West, 30% South, 20% Northeast, 13% Midwest, and 5% Canada). (The mean number of patients per center was 5 [median: 3]. Seventy-three percent of the total population was pediatric, including 68% thalassemia major patients and 79% thalassemia intermedia patients.) The ethnicity of the population was 50% Asian, 30% white, and 20% Middle Eastern/other.

DISCUSSION

Recently, the ethnicity, age distribution, and genotypes of North American patients affected by severe

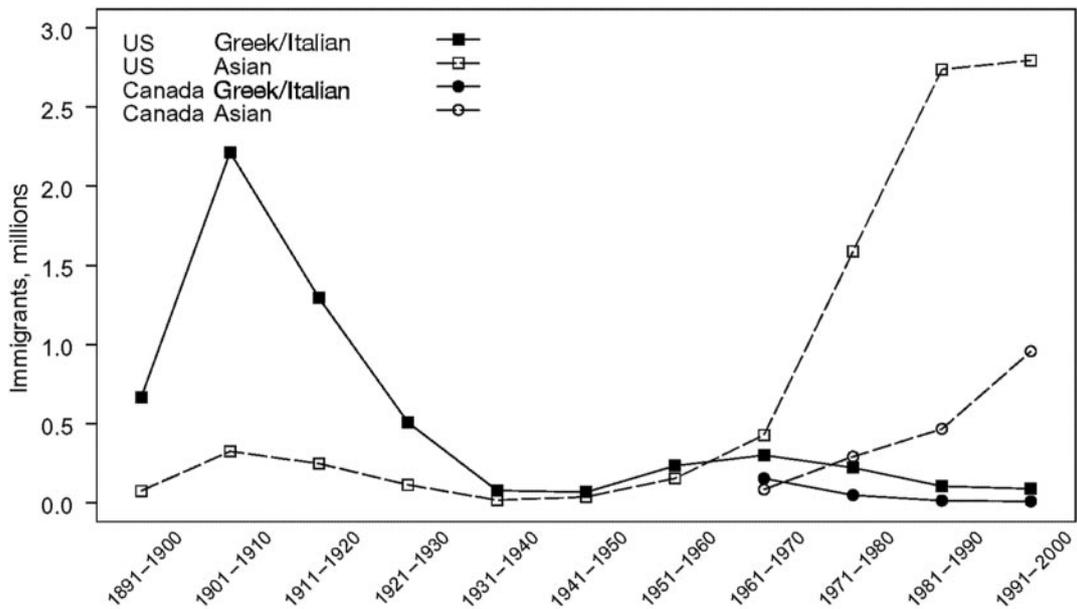


Fig 4. Ethnicity of US and Canadian immigration over the last 100 years: census data from the US and Canada document the changing pattern of immigration for Greek/Italian and Asian populations over the past 100 years.¹⁶

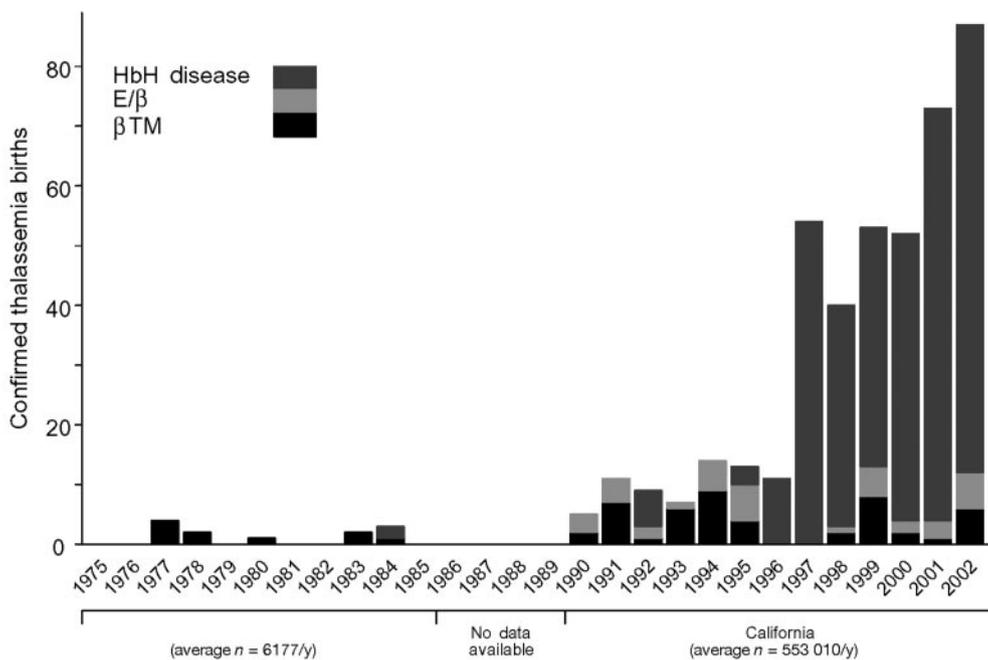


Fig 5. Newborn-screening data: confirmed thalassemia births in California from 1975 to 2003. Hemoglobin H disease, E- β -thalassemia, and β -thalassemia are indicated. Data were obtained from the State Department of Human Services, Genetics Laboratory. From 1990 to present, the hemoglobin genotype was determined by high-pressure liquid chromatography, followed by DNA confirmation; from 1975 to 1989, diagnosis was confirmed by isoelectric focusing.

TABLE 4. Ethnicity of Patients With β -Thalassemia From the Greater Toronto Area as a Function of Decade of Birth

Population	<1961	1961-1970	1971-1980	1981-1990	1991-2004
Southern European (Italian, Greek), %	50	59.0	65.5	27.4	21.1
Middle Eastern, South Asian, Southeast Asian, %	50	41.0	34.5	59.6	78.9
Total no. of patients	24	39	55	62	71*

Data are from McMaster University Medical Centre.

* Thirty-seven additional cases of homozygous β -thalassemia were detected by prenatal diagnosis during this time period, all from couples referred from the Greater Toronto Area.

thalassemia have changed dramatically.^{3,13,14,17} Declining immigration from Mediterranean regions, effective genetic counseling programs, and improved therapy have resulted in Mediterranean patients being underrepresented in pediatrics and disproportionately found among older survivors. In contrast, immigration from Asia^{3,6,7,18} has increased 2000% between the 1960s and the 1990s (Fig. 4). The immigration of this high-risk population is responsible for the recent increase in patients with thalassemia detected in newborn-screening programs. In parallel with these changing demographic patterns, the disease genotypes have also been altered. The formerly less well-examined syndromes of hemoglobin H and E- β -thalassemia, arising primarily in immigrants of Asian or Indian/Middle Eastern descent, have acquired proportionally greater clinical importance and account for 28% of the population reported in this study. The changing pattern of ethnicity extends beyond E- β -thalassemia and α -thalassemia; 60% of the children affected by thalassemia major, a disorder historically affecting white people in North America, are from other ethnic backgrounds, reflecting the high birth rate of affected children in some areas of Asia and India, in which β^0 -thalassemia has been reported to occur in 1 of every 2000 births.³ The hemoglobinopathy programs from California and Ontario, 2 regions with the most patients with thalassemia, illustrate the effects of immigration on the number and ethnicity of thalassemia births. Thalassemia can no longer be termed a "Mediterranean anemia."¹⁹

What are the implications of this analysis for management of thalassemia in North America? Clearly, attention to the screening, diagnosis, and management of E-thalassemia is indicated: hemoglobin E is the most common hemoglobin variant worldwide, with an incidence of the most severe phenotype, hemoglobin E-thalassemia, of 1 in 2200 births among Southeast Asians.^{20,21} Little is understood about the variable phenotype of this genotype, an issue that deserves more study.^{14,20,22} Similarly, although hemoglobin H disease was once considered to be a relatively benign condition, variants are more severe than originally considered.²³ One third of our patients with hemoglobin H-Constant Spring disease receive transfusions. Hemoglobin H-Constant Spring is considered a public health problem in California and requires neonatal screening.¹⁸ Finally, homozygous α -thalassemia, previously considered uniformly fatal, is increasingly associated with survival throughout childhood; 7 such patients are included in this report.²⁴ Homozygous α -thalassemia will be diagnosed more often before birth because of advances in diagnostic and interventional obstetric technology, and a greater understanding of this disease also needs urgent attention.

The optimal approach to treatment of thalassemia syndromes in this population is uncertain. Transfusions, stem cell transplantation, hemoglobin-F chemotherapy, and preimplantation diagnosis are therapeutic options available for families. However, lack of clear genotype-phenotype correlations create a dilemma in decision-making. Although heterogeneity

in phenotype cannot be totally explained by the globin mutations, adequate genotyping will allow for useful phenotypic predictions. For example, comprehensive genotyping would enable parents of a newborn homozygous for the β -globin codon 39 nonsense mutation without α -thalassemia to receive education about chronic transfusion therapy and stem cell transplantation before the child became ill. The morbidity from delayed diagnosis of hemoglobin-H Constant Spring and syndromes with excess α genes or dominant β -thalassemia alleles could be prevented also. Genotyping also permits separation of homozygous E, a benign condition, from E- β^0 -thalassemia. Hemoglobinopathy-screening programs should use genotyping methods. High-throughput multiplex DNA techniques can cost-effectively screen for common European and Asian α -globin and β -globin alleles, as well as genetic modifiers, that account for the majority of hemoglobinopathies observed in our population.²⁵⁻²⁷

New developments in the monitoring and treatment of thalassemia have redefined the definition of adequate care for these diseases. These complex standard-care guidelines will require a close working relationship between thalassemia centers and the growing number of smaller patient programs in North America.²⁸ Thalassemia, often considered a pediatric disease, has become a chronic adult illness with a median life span approaching 40 years in North America. Fertility and other complex medical problems associated with older patients need to be addressed. Linguistic isolation and socioeconomic barriers, often associated with immigrant populations, impair the ability to implement comprehensive care and necessitate trained counselors and translators. A multidisciplinary approach that addresses the changing treatment and epidemiology of thalassemia will ensure improved quality of life and survival.

ACKNOWLEDGMENTS

This work was supported by a cooperative agreement with the National Heart, Lung, and Blood Institute, National Institutes of Health (U01-HL-65232 to Children's Hospital of Philadelphia; U01-HL-65233 to University Health Network Toronto General Hospital; U01-HL-65239 to Children's Hospital and Research Center; U01-HL-65244 to Weill Medical College of Cornell University; U01-HL-65260 to Children's Hospital Boston; and U01-HL-65238 to New England Research Institutes) and in part by National Institutes of Health grant M01-RR01271 to the Pediatric Clinical Research Center.

We thank Jeanna Brushwood and Jeanyoung Kim for providing editing and manuscript preparation.

The following institutions and researchers contributed to the Thalassemia Clinical Research Network Registry data reported in this article. Toronto General Hospital: Nancy F. Olivieri, MD, principal investigator (satellite: Hospital for Sick Children); DNA Diagnostic Laboratory for the Hemoglobin Disorders (Hamilton, Ontario, Canada): John S. Wayne, PhD; Children's Hospital of Philadelphia: Alan Cohen, MD, principal investigator (satellites: St Christopher's Children's Hospital and Children's Memorial Hospital [Chicago, IL]); Weill Medical College of Cornell University: Patricia Giardina, MD, principal investigator (satellites: Columbia Presbyterian Medical Center, Schneider Children's Hospital, Long Island College Hospital, New York Methodist Hospital, Hackensack Hospital, and Winthrop University Hospital); Children's Hospital at Oakland: Elliott Vichinsky, MD, principal investigator (satellites: Children's Hospital Central California, Children's Hospital of Los Angeles, University of California San Francisco, Children's Hospital of Orange County, Lucile Packard Children's

Hospital); Children's Hospital Boston: Ellis Neufeld, MD, PhD, principal investigator, and Melody J. Cunningham, MD, coinvestigator; Genetic Disease Branch, California Department of Health Services, Berkeley: Fred Lorey, PhD, Chief, Program Department and Evaluation Section; Network Steering Committee Chair, David Nathan, MD; National Heart, Lung, and Blood Institute oversight: Charles Peterson, MD; and Data Coordinating Center: New England Research Institutes (Eric Macklin, PhD, and Libby Wright, PhD).

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Pediatrics 2005;116:e818

DOI: 10.1542/peds.2005-0843 originally published online November 15, 2005;

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The online version of this article, along with updated information and services, is located on the World Wide Web at:

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