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Thalassemia in Canadians

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Thirteen Canadians with a mild hypochromic anemia were found to have beta thalassemia trait. The families of these individuals had resided in Canada for two to five generations and, where known, had not emigrated from areas with a high incidence for the thalassemia gene. A Negro family with abnormal erythrocyte morphology was suspected to be carrying the thalassemia gene although the hemoglobin A_2 concentration was normal and abnormal minor components were not detected. Thalassemia trait has been detected in practically every ethnic group, and its sporadic occurrence among Canadians without Mediterranean ancestry can be expected.

Chez 13 canadiens qui présentaient une anémie hypochrome bénigne, on a découvert la tare héréditaire de thalassémie bêta. Les familles de ces sujets avaient résidé au Canada depuis plusieurs générations (deux à cinq) et, quand on le savait, n'avaient pas émigré de régions où la fréquence du gène thalassémique est forte. Chez les membres d'une famille de nègres dont le sang comportait des érythrocytes de morphologie anormale, on soupçonna la présence de gène thalassémique, bien que la concentration d'hémoglobine A_2 ait été normale et qu'on n'ait pu déceler des éléments mineurs anormaux. La tare thalassémique existait dans virtuellement tous les groupes ethniques et on peut s'attendre à son apparition sporadique parmi les canadiens n'ayant aucun ancêtre d'origine méditerranéenne.

IN 1955, Israels, Suderman and Hoogstraten[1] reported the occurrence of thalassemia in a family originally from Scotland who lived in Canada. Subsequently, thalassemia trait has also been noted sporadically in England,[2-4] Scotland,[5] Germany[6] and Australia[7] in individuals without known Mediterranean ancestry. These observations, together with the known areas in the Mediterranean region, India, China and South America, indicate a world-wide distribution of the thalassemia gene.[8] The purpose of this paper is to record the occurrence of thalassemia trait in 16 individuals in six Canadian families. Thirteen individuals in five families had beta thalassemia trait and one Negro family had abnormal erythrocyte morphology similar to that seen in thalassemia. Thalassemia trait may be more common than has been suspected among Canadians without known Mediterranean ancestry.

METHODS

Hemoglobin was determined as cyanmethemoglobin[9] and red cell counts with the Coulter Model A electronic counter. Serum iron, iron binding capacity,[10] alkali resistant hemoglobin[11] and osmotic fragility[9] were as described. Prussian blue stains[9] of bone marrow showed increased hemosiderin[12] in all propositi. Starch gel electrophoresis was performed by the method of Smithies[13] as modified by Boyer.[14] Quantitative determination of hemoglobin A_2 was as described.[15]

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CASE REPORTS

Family Pr.—The propositus (B.Pr.) was a 12-year-old male who was found to have a hypochromic anemia on a routine hematological study during investigation of headache. The laboratory data for this family are recorded in Table I. Both the father (F.Pr.), who had received iron therapy for many years for a mild hypochromic anemia, and the paternal grandmother (M.Pr.), who was well, were found to have an elevated hemoglobin A_2 on starch gel electrophoresis. The hemoglobin A_2 concentration was normal in the mother of the propositus. The parents and grandparents of M.Pr. were residents of Nova Scotia. There was thus no known Mediterranean ancestry in five generations in this family.

Family Hn.—The propositus (G.Hn.) was a 25-year-old nurse in whom hypochromic anemia had been detected in Quebec, during her nursing course. She took oral iron for the next four years until an aspirate of her bone marrow showed hemosiderosis. The laboratory findings for this family are recorded in Table I. The propositus and her mother (E.Ln.), who resides in Ontario, were found to have an elevated concentration of hemoglobin A_2. Hemoglobin A_2 concentrations were normal in the father. The mother (E.Ln.) and maternal grandmother and grandfather of the propositus were born in Canada and Mediterranean ancestry was unknown for three generations.

Family He.—The propositus (R.He.), a 38-year-old office manager, was found to be anemic in 1939 when volunteering as a blood donor. He was treated with oral iron preparations on several occasions during the next 24 years because of mild fatigue and a persistent hypochromic anemia. The laboratory findings on the propositus and his son (L.He.), both

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TABLE I.

Family	*Patient*	*Sex*	*Hemoglobin (g.%)*	*Mean cell hemoglobin (μg.)*	*Saturation of transferrin (%)*	*Concentration hemoglobin A_2 (%)*	*One-minute alkali resistant hemoglobin (%)*
Pr.	B.Pr.	M	11.5	20.1	28	6.4	1.9
	F.Pr.	M	12.6	23.5	—	4.8	—
	M.Pr.	F	11.6	22.6	—	5.3	2.0
Hn.	G.Hn.	F	10.1	21.8	64	5.8	2.3
	E.Ln.	F	—	—	—	5.4	—
He.	R.He.	M	12.1	18.9	47	5.4	1.6
	L.He.	M	12.1	19.7	24	3.7	4.1
Mn.	T.Mn.	F	10.7	20.1	52	5.0	1.9
	P.Bn.	M	12.0	—	—	4.6	0.8
Hr.	P.Hr.	F	11.7	20.6	27	3.5	1.3
	R.Nk.	F	13.5	20.3	—	4.1	—
	G.Mr.	F	11.5	—	—	4.3	—
	E.Mr.	M	10.4	—	—	4.4	—
Cy.	J.Jn.	F	11.6	30.6	—	2.3	0.8
	L.Cy.	F	10.6	—	—	Normal*	—
	E.Cy.	M	14.5	27.3	—	2.5	0.8
Normal	Mean			31.0	38	2.2	
	S.D.†			1.0	10	0.35	<2.0

*By appearance on starch gel.
†Standard deviation.

of whom had elevated hemoglobin A_2 concentrations, are recorded in Table I. The propositus' maternal and paternal grandparents and great-grandparents had been residents of Nova Scotia and Newfoundland, and Mediterranean ancestry could not be identified in three generations.

Family Mn.—The propositus was a 40-year-old housewife. Routine hematological studies had disclosed a hypochromic anemia in 1954. She had received oral and intramuscular iron on several occasions during the next 10 years. The propositus (T.Mn) and her father (P.Bn.) had an elevated concentration of hemoglobin A_2 (Table I). The hemoglobin A_2 concentration was normal in the mother. P.Bn. had been known to be anemic for many years. The grandparents of P.Bn. had emigrated to Canada from Scotland. There was no known Mediterranean ancestry in four generations.

Family Hr.—The propositus was a 31-year-old secretary. Anemia was first detected at age 25, and on occasion during the next six years she had taken iron-containing preparations. The laboratory findings in the propositus (P.Hr.), her mother (R.Nk.), sister (G.Mr.), and the sister's son (E.Mr.), all of whom had elevated concentrations of hemoglobin A_2, are shown in Table I. The concentration of hemoglobin A_2 was normal in the father of the propositus. R.Nk.'s mother, father and paternal grandparents were Canadian. R.Nk.'s maternal grandmother was Swedish; the maternal grandfather was believed to be Spanish.

Family Cy.—The propositus was a 38-year-old Negro female. A routine chest radiograph in December 1963 had disclosed an infiltration in the right upper lobe, and tubercle bacilli were grown from her sputum. The hemoglobin was 9.6 g. %, numerous target cells were present on the blood smear and the erythrocytes were resistant to osmotic hemolysis at this time. There was moderate hemosiderosis of the bone marrow. She was hospitalized for treatment of the pulmonary tuberculosis for 17 months. The hematological studies were repeated in 1966 and are recorded in Table I. The propositus (J.Jn.), her mother (L.Cy.) and brother (E.Cy.) had large numbers of target cells in the peripheral blood. Target cells comprised 38% and 31% of the propositus' and her brother's erythrocytes, respectively. Osmotic hemolysis began at 0.45% NaCl and 50% hemolysis occurred at 0.35% NaCl in J.Jn. The corresponding figures for E.Cy. were 0.45 and 0.375% NaCl. Hemoglobin electrophoresis of J.Jn. and E.Cy. on filter paper with a barbital buffer at pH 8.6 and a phosphate buffer at pH 6.5 showed a single band having the mobility of hemoglobin A. Cellulose acetate electrophoresis at pH 8.6 in a tris-EDTA-borate buffer showed a major and a minor band having the mobility of hemoglobin A and A_2. Vertical starch gel electrophoresis at pH 8.3 in a tris-citrate-borate buffer in J.Jn., L.Cy. and E.Cy. showed a major and a minor band corresponding to hemoglobin A and hemoglobin A_2.* The concentration of hemoglobin A_2 was 2.3% in J.Jn. and 2.5% in E.Cy. In this system with a 0.0054 M phosphate buffer at pH 7.0 there was a single band with the mobility of hemoglobin A. Minor components (hemoglobin H and Barts) were not detected. No intra-erythrocyte inclusions were demonstrable after three hours' incubation in brilliant cresyl blue.

DISCUSSION

The population genetics of thalassemia has been recently reviewed by Chernoff.[8] The defect may have arisen from a single focus in the northern Mediterranean. Probably as the result

*Kindly performed by Dr. Margaret DeWolfe.

of migration, other major areas of the disease developed on the eastern shores of the Mediterranean and in India, China and the United States. Sporadic cases in other areas are more likely to have occurred through further migration, although spontaneous mutation cannot be excluded. These sporadic cases of thalassemia have a world-wide distribution and have been recognized in practically every ethnic group.[16]

Thalassemia was first recognized in Canadians by Israels, Suderman and Hoogstraten[1] in a family who emigrated to Canada from Scotland. Siddoo *et al.* identified thalassemia in Chinese Canadians[17] and in Sikhs[18] in British Columbia, and Rioux and Delage[19] in three families in Quebec. One of these families had no known Mediterranean ancestry and had resided in Quebec for more than two centuries. In recent years, thalasemia has been found in many immigrants to this country from the known high incidence areas. It has been recorded, however, in only two Canadian families without known Mediterranean ancestry.[1, 19]

In the present study, family Pr. had lived in Canada for five generations and families Hr. and He. for three. These families were unable to trace their family origins further back. The great-grandparents of the propositus of family Hn. had emigrated to Canada from Scotland, and Mediterranean ancestry was unknown. Family Hr. had Swedish and possibly Spanish ancestry four generations previously. None of the ancestors of these four families were known immigrants from high incidence areas for the thalassemia gene. Since thalassemia has been identified in most of the countries from which Canada drew its early settlers, including England[3-5] and Scotland,[1, 2] the sporadic occurrence of the defect in this country would be expected even in those who have not migrated from areas of known high incidence.

The interaction of the thalassemia gene with known alpha and beta hemoglobin chain variants has led to the recognition of alpha and beta thalassemia. The hemoglobin A_2 concentration is elevated in more than 90% of cases of beta thalassemia trait.[20] In infants with alpha thalassemia trait hemoglobin Barts or traces of hemoglobin H may be detected,[16] although these hemoglobins probably infrequently persist into adult life. Because of the absence of a consistent biochemical abnormality in adult thalassemia trait, it is difficult to classify families who have thalassemia-like morphological changes in erythrocytes but without elevated hemoglobin A_2 and in whom hemoglobin H or Barts is not demonstrable. Because the Nova Scotia Negro population developed from migrations from the United States[21] in whom alpha thalassemia trait appears to be more common,[22] family Cy. might have been expected to carry this gene. In the absence of hemoglobin H or Barts and results from neonates in this family, it is impossible to make this distinction.

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