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Arteriosclerotic Events Are Less Frequent in Persons with Chronic Anemia: Evidence from Families with Hereditary Spherocytosis

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Because anemic persons have lower cholesterol and whole blood viscosity than those who are not anemic, we hypothesized that subjects with hereditary spherocytosis who have not had the spleen removed should have fewer arteriosclerotic events than unaffected family members. We defined arteriosclerotic events as myocardial infarct, stroke, coronary artery surgery, and carotid artery surgery. We compared the rate of these events in affected–not splenectomized persons to the rate in unaffected family members. The relative risk of an arteriosclerotic event in hereditary spherocytosis patients with a spleen was one fifth that in unaffected family members. These data support the hypothesis that chronic anemia retards the development of arteriosclerosis. Spherocytosis is another example of an inherited condition that conveys an advantage in one system and a disadvantage in another. Am. J. Hematol. 81:315–317, 2006. © 2006 Wiley-Liss, Inc.

Key words: anemia; arteriosclerosis; cholesterol; hereditary spherocytosis; myocardial infarction; stroke

INTRODUCTION

Anemia, even when mild, is associated with low serum cholesterol [1–3]. In the Framingham study, subjects with a hemoglobin concentration below the group median had a stroke rate less than half that in subjects with hemoglobin concentration above the median [4]. Another set of Framingham data [5] and a study from Stockholm [6] showed that the rate of myocardial infarcts was lower in subjects with lower hemoglobin levels. Two reports indirectly demonstrate that thalassemia trait, also a mild anemia accompanied by low cholesterol, is associated with a decreased likelihood of myocardial infarction [7,8]. We hypothesized that the combination of lower cholesterol and lower whole blood viscosity found in anemia should result in a reduction of arteriosclerotic (AS) events in persons with hereditary spherocytosis who have not undergone splenectomy. Because of a long-term commitment to the care and study of hereditary spherocytosis patients [9–15], we have information about the medical history of a large number of family members.

METHODS

A priori, members of hereditary spherocytosis families comprise three subsets: (1) not affected; (2) affected–spleen in; (3) affected-spleen out. We report a retrospective study comparing the rate of arteriosclerotic events in unaffected family members to the rate in affected subjects who have not had a splenectomy. Our database includes 687 persons from 35 putatively unrelated kindreds. There are 624 persons for whom we are confident of the classification as affected or not. The 63 persons for whom we

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TABLE I. Rates and Relatives Risk of Arteriosclerotic Events: (A) Cumulative Percentage of Persons Having an AS Event at Several Ages in the Two Groups (Kaplan–Meier estimate); (B) Relative Risk of an AS Event (Cox Proportional Hazards Model)

(A) Rates of Arteriosclerotic Events (95% CI)			
Age	U (unaffected)	A (affected/spleen-in)	U−A (difference)
50	1.5% (0.0%, 3.6%)	1.0% (0.0%, 3.1%)	0.5% (−2.4%, 3.5%)
60	5.0% (0.5%, 9.3%)	1.0% (0.0%, 3.1%)	4.0% (−0.9%, 8.9%)
70	13.8% (5.0%, 21.8%)	1.0% (0.0%, 3.1%)	12.7% (4.1%, 21.4%)
80	30.1% (15.0%, 42.6%)	12.8% (0.0%, 24.6%)	17.3% (−1.3%, 36.0%)
90	46.0% (22.7%, 62.3%)	12.8% (0.0%, 24.6%)	33.2% (10.1%, 56.3%)
(B) Relative Risk (RR 95% CI) of First Arteriosclerotic Event (Cox Proportional Hazard Ratio)			
Affected vs. unaffected			0.21 (0.07, 0.63)

are unsure of the classification are not considered in this report.

Arteriosclerotic events were defined in advance as a history of at least one of the following: myocardial infarction, stroke, or coronary or carotid artery surgery. Since no one had an AS event before age 40, we compared the rate of first AS events after age 40 in the unaffected group to the rate after age 40 in the affected-spleen in group.

Considering only those persons who have reached age 40, there were 145 (66 male, 79 female) unaffected and 129 (74 male, 55 female) affected-spleen in. In the affected group, 34 subjects (21 male, 13 female) had their spleen removed after age 40 and were censored at that time, leaving 95 affected subjects (53 male, 42 female) who completed the study. The 147 subjects who had the spleen removed before age 40 were not considered in this report. A previous publication from this institution [15] demonstrates that subjects who have had a splenectomy for spherocytosis have a fivefold greater rate of AS events than those who have not had a splenectomy.

Our database includes dates of birth, death, first AS event, splenectomy, and last contact. Family members were interviewed by one of the authors (RFS) in person, via phone, fax, e-mail, or paper mail. In the inevitable instances where exact dates for splenectomy and AS event could not be recalled we estimated the date from information supplied by the patient or a family member, e.g., an event that occurred "in the summer of 1960" was dated 15 July 1960. Hospital records or physician's reports were reviewed in some instances. The subjects were asked about myocardial infarction, stroke, and coronary and carotid artery surgery. The subjects were encouraged to offer other medical history and ask medical questions. We have information about diabetes and hypertension for some of the subjects.

Calculations were made by two methods. The cumulative event rates for the two groups were calculated with the Kaplan–Meier method. The Cox proportional hazards model was used to estimate differences between the groups. The Cox model included the year of birth to capture cohort effects.

RESULTS

Twenty of the 145 unaffected subjects over age 40 had at least one AS event. Four of the 129 affected subjects over age 40 with the spleen in had at least one AS event. Kaplan–Meier estimates of the cumulative event rate for several ages are shown in part A of the Table and are plotted in Figure 1. The rate of AS events is much lower in affected subjects with a spleen than in unaffected family members. The Cox estimate of the proportional hazard ratio is presented in part B of the Table. Hereditary spherocytosis subjects with a spleen have approximately one fifth the risk of those who did not inherit spherocytosis. Estimates from a second Cox model that included gender as a covariate did not differ appreciably from the estimates in the Table.

DISCUSSION

Several caveats should be noted about the data in this report. The total number of AS events is not great, but when expressed as rates the difference between the two groups is large, and each of the two methods of analysis shows, with a robust degree of confidence, that AS events are significantly less frequent in affected subjects with a spleen.

Smoking, hypertension, diabetes, and elevated cholesterol are important risk factors for AS events. We have no data about smoking habits. With respect to hypertension, 25% (27/108) of the unaffected

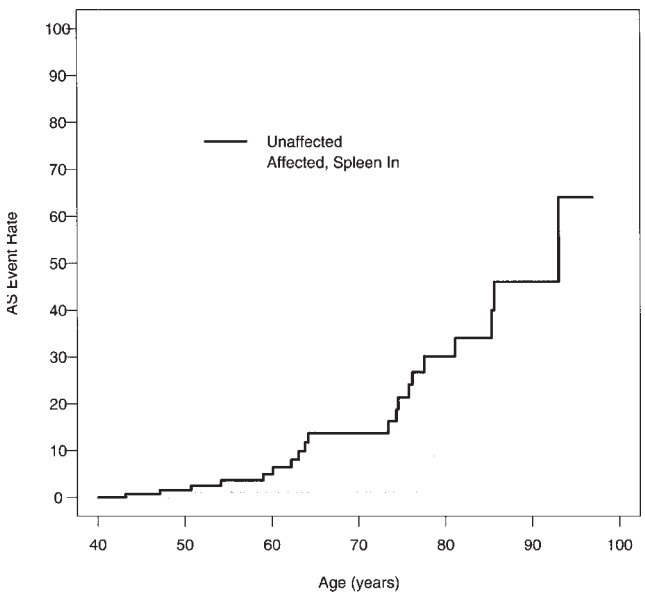

Fig. 1. Cumulative incidence (%) of arteriosclerotic events by age. Kaplan-Meier estimate of the cumulative incidence (%) of arteriosclerotic events by age in subjects without spherocytosis (unaffected) and with spherocytosis who have not undergone splenectomy (affected-spleen in). All subjects are members of affected families.

subjects are hypertensive compared with 26% (16/61) of the affected-spleen in subjects. As for the prevalence of diabetes, 16% (13/79) of the unaffected subjects and 14% (7/49) of the affected-spleen in subjects are diabetic. Although we do not have information on hypertension and diabetes in all subjects, the available data do not indicate an excess of hypertension or diabetes in the unaffected group, nor are we aware of empirical data to suggest that the genotypes known to cause phenotypic spherocytosis decrease the likelihood of diabetes and hypertension.

Based on previous reports of these families, affected persons who had not had the spleen removed had mild anemia; their average hemoglobin was less than 2 g/dl lower than in unaffected family members [9,11,13]. It has been well documented that the serum cholesterol is low in spherocytosis patients before splenectomy, and it is a general phenomenon that cholesterol rises following successful therapy of anemia [1,2]. Therefore, it is a tenable assumption that anemia is a cause of low cholesterol. Anemia also reduces whole blood viscosity. It seems reasonable to attribute the reduced rate of AS events seen in this study to the adjustments in biochemistry and physiology made in response to the anemia of hereditary spherocytosis.

The data presented here confirm previous reports indicating that subjects with lower hemoglobin levels have fewer arteriosclerotic events than subjects with a higher hemoglobin. The magnitude of the difference we have found suggests that lifelong mild anemia reduces arteriosclerotic events to an impressive degree. Spherocytosis is another example of a hereditary condition that brings a benefit in one sphere and a disadvantage in another.

REFERENCES

1. Rifkin BM, Gale M. Hypolipidaemia in anaemia: implications for the epidemiology of ischemic heart disease. Lancet 1967;ii: 640–642.
2. Westerman MP. Hypocholesterolaemia and anaemia. Br J Haematol 1975;31:87–94.
3. Elwood PC, Sweetnam P, Welsby E, Mahler R, Moore F. Association between circulating haemoglobin level, serum-cholesterol, and blood-pressure. Lancet 1970;1(7647):589–590.
4. Kannel WB, Gordon T, Wolf PA, McNamara P. Hemoglobin and the risk of cerebral infarction: the Framingham study. Stroke 1972;3:409–419.
5. Gagnon DR, Zhang TJ, Brand FN, Kannel WB. Hematocrit and the risk of cardiovascular disease – the Framingham study: a 34-year follow-up. Am Heart J 1994;127:674–682.
6. Bottiger LE, Carlso LA. The Stockholm Prospective Study 2. In: Waldenstrom J, Larsson T, editors. In early phases of coronary heart disease: the possibility of prediction. Ljungstedtn, Stockholm: Nordiska Bokhandelns Forlag; 1973. pp 158–181.
7. Crowley JP, Sheth S, Capone RF, Schilling RF. A paucity of thalassemia trait in Italian men with myocardial infarction. Acta Haematol 1987;78(4):249–251.
8. Chang C, Schilling RF. Myocardial infarction and thalassemia trait: an example of heterozygote advantage. Am J Hematol 1995; 49:73–75.
9. MacKinney AA Jr., Morton NE, Kosower NS, Schilling RF. Ascertaining genetic carriers of hereditary spherocytosis by statistical analysis of multiple laboratory tests. J Clin Invest 1962;41:554–567.
10. Morton NE, MacKinney AA Jr., Kosower NS, Schilling RF, Gray MP. Genetics of spherocytosis. Am J Hum Genet 1962;14:170.
11. MacKinney AA Jr. Hereditary spherocytosis: clinical family studies. Arch Intern Med 1965;116:257–265.
12. Shahidi NT, Clatanoff DV. The role of puberty in red-cell production in hereditary haemolytic anaemias. Br J Haematol 1969; 17(4):335–342.
13. Schilling RF. Hereditary spherocytosis: a study of splenectomized persons. Semin Hematol 1976;13:169–176.
14. Schilling RF. Estimating the risk for sepsis after splenectomy in hereditary spherocytosis. Ann Intern Med 1995;122:187–188.
15. Schilling RF. Spherocytosis, splenectomy, strokes, and heart attacks. Lancet 1997;350:1677–1678.