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Pyridoxine Responsive Hereditary Sideroblastic Erythropoiesis and Iron Overload: Two Microcytic Subpopulations in the Affected Male, One Normocytic and One Microcytic Subpopulation in the Obligate Female Carrier

John W. Harris, Elizabeth H. Danish, Gary M. Brittenham, and Christine E. McLaren

Departments of Medicine and Pediatrics, Case Western Reserve University, School of Medicine at MetroHealth Medical Center, 2500 MetroHealth Drive, R369, Cleveland, Ohio

Mild hepatic iron overload has been demonstrated by magnetic susceptibility measurements in a 22-year-old man with hereditary sideroblastic erythropoiesis despite hemoglobin levels in the normal range and a normal erythropoietin level. His grandfather's sideroblastic anemia has been found to be responsive to pyridoxine; his mother's hemoglobin has persisted in the normal range but red cell volume distribution analysis demonstrated two subpopulations; 30% with estimated geometric mean of 68 fl and 70% an estimated mean of 93 fl. Red cell distribution analysis of the grandson demonstrated *two* microcytic subpopulations; 46% with an estimated geometric mean of 45 fl and 54% an estimated mean of 70 fl. A therapeutic regimen is outlined to reduce to normal his iron stores and to prevent the future development of excessive iron overload. © 1993 Wiley-Liss, Inc.

Key words: pyridoxine, iron overload, microcytic, normocytic sideroblastic erythropoiesis

In 1962, severe sideroblastic anemia in a 44-year-old white woman and moderately severe sideroblastic anemia in her 43-year-old brother were reported [1] and repeatedly demonstrated to be responsive to pyridoxine. Microcytic changes had been documented for 32 and 15 years, respectively, and persisted despite achieving normal hemoglobin levels. No hematologic abnormalities were then found in the patients' mother, sister, six paternal and two maternal cousins, and five children.

In July 1982, the brother's 13-year-old grandson was found to have microcytosis, MCV-65 fl and a cellular bone marrow with 67% of the erythroid series as ringed sideroblasts: hemoglobin, 12.3 g/dl; serum iron, 162 μg/dl; total iron binding capacity, 302 μg/dl; percentage saturation, 53; serum ferritin, 97 μg/L; FEP, 33 μg/dl RBC; normal B_{12}, folate, and hemoglobin analyses. Red cell volume distribution analysis [2] demonstrated *two* microcytic subpopulations: 46% with an estimated geometric mean of 45 fl, and 54% with an estimated geometric mean of 70 fl. At that time, his mother had an MCV-87 fl; hemoglobin, 14.8 g/dl; serum iron, 135 μg/dl; total iron binding capacity, 375 μg/dl; percentage saturation, 36; serum ferritin, 33 μg/L; FEP, 43.0 μg/dl RBC, and normal hemoglobin analyses. Volume distribution analysis of her red cells demonstrated two subpopulations: 30% with an estimated geometric mean of 68 fl and 70% with an estimated geometric mean of 93 fl.

The grandson was next seen in December 1990 at age 22, having in the interval experienced good health with no limitations because of his abnormal hematologic findings. Except for one week during which one Feosol tablet t.i.d. was ingested, no hematinics were taken. His MCV was 68 fl; hemoglobin, 12.2 g/dl; reticulocytes, 1.1%; serum iron, 151 μg/dl; total iron binding capacity, 246 μg/dl; percentage saturation, 59; and serum ferritin, 528 μg/L. The serum erythropoietin level was 11 mU/ml (normal range 1–18 mU/ml) (Table I). Hepatic storage iron determination by magnetic susceptibility yielded a value of 2,555 ± 267 μg Fe/g liver (wet weight) (upper confidence level for normal adult males is 480 μg/g liver).

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Address reprint requests to John W. Harris, M.D., MetroHealth Medical Center, 2500 MetroHealth Drive, Research 369, Cleveland, OH 44109-1998.

TABLE I. Hematologic Values and RBC Volume Distributions

	Mother		Son	
	1982	1990	1982	1990
MCV (f)	87	87	65	68
RBC volume distribution	30% @ 68 fl 70% @ 93 fl		46% @ 45 fl 54% @ 70 fl	
Hb (g/dl)	14.8	13.3	12.3	12.2
Serum erythropoietin (mU/ml)		6		11
Fe (μg/dl)	135	97	162	151
TIBC (μg/dl)	375	349	302	246
% Sat	36	28	53	59
Ferritin (μg/L)	33	15.7	97	528
Retics (%)		1.3		1.1
FEP (μg/dl RBC)	43		33	

Based on serum ferritin and circulating hemoglobin levels, in 9 years his body iron had increased from an initial value of 2.03–6.32 g. Since growth and expanded RBC mass would contribute an increment of 0.99 g, an excess iron accumulation of 3.30 g is indicated. Should this rate be allowed to persist, about 2 g of excess iron would be added to his body stores every 5 years; should the rate of absorption that occurred during his growth phase persist, a minimum of 2.5 g would be added every 5 years. At age 52, he then would have added some 12 or 15 g of iron to his already abnormal body burden.

It is noteworthy that his hemoglobin has consistently been at, or just below, the lower normal limits for age, while the one erythropoietin determination was within normal limits. Presumably, a stimulus for enhanced iron absorption is the component of ineffective erythropoiesis due to the sideroblastic changes in erythroid production.

Previous reports of red cell volume distribution analyses in affected males have found only one microcytic population [2,3] or a subpopulation of microcytic cells along with a major population of normocytic cells [2]. Previous reports documenting excess iron accumulation have been in patients with sideroblastic anemias of severe or mild degree, usually managed by transfusions and found to be nonresponsive to pyridoxine [4–6]. A regimen of pyridoxine and venesections is under way, with careful documentation of the amount of iron removed to confirm the above assumptions and calculations.

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