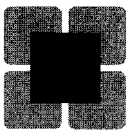

Familial polycythemia vera

ROBIN L. MILLER, MD; JOSEPH D. PURVIS III, MD; JAMES K. WEICK, MD

■ The occurrence of polycythemia vera in a father, mother, and two sons is reported. Thirteen kindreds with familial polycythemia vera in 31 members are reviewed. Comprehensive records were available for all four patients as well as other family members, since all were diagnosed and treated at the authors' institution over a period of nearly 50 years. The mean age at diagnosis, sex predominance, symptoms, and incidence of chromosomal abnormalities, leukocytosis, thrombocytosis, and elevated leukocyte alkaline phosphatase levels were similar to those of nonfamilial cases. The mean RBC volume at diagnosis and the incidence of splenomegaly appear to be higher in familial than nonfamilial cases. The mode of inheritance is unclear, but genetic factors may be involved in the pathogenesis of this myeloproliferative disorder.

□ INDEX TERM: POLYCYTHEMIA VERA □CLEVE CLIN J MED 1989; 56:813–818

DOCUMENTED cases of familial polycythemia vera are rare and insufficient to implicate a common genetic defect or basis of inheritance.[1–9] While numerous reports of familial polycythemia have appeared since 1907, most cases lack modern diagnostic criteria for primary polycythemia vera and, upon careful scrutiny, are better classified as secondary polycythemia due to either an altered hemoglobin molecule or abnormal erythropoietin production and regulation.[10]

True primary polycythemia or polycythemia rubra vera is a clonal, myeloproliferative disorder affecting erythrocytes, neutrophils, and platelets.[11] Its cause is unknown; however, genetic and environmental factors have been implicated.[12] The increased frequency of polycythemia vera among Jews,[13] its decreased frequency in blacks,[12] the occurrence of nonrandom chromosomal abnormalities,[14–17] and the rare reports of familial cases[1–9] suggest at least some genetic role in its etiology.

Our cases represent, to our knowledge, the largest familial clustering of polycythemia vera reported to date. The affected patients span two generations and include a mother, father, and two sons. *Figure 1* illustrates the affected family's pedigree. They were all Roman Catholics of German and Bavarian ancestry. Comprehensive records were available for all four patients as well as other family members, since all were diagnosed and treated at our institution over a period of nearly 50 years. This unique family lends further support to the theory that there is some genetic predisposition in the etiology of the myeloproliferative disorders. Continued surveillance of the kindred may further illuminate this mode of inheritance.

From the Department of Hematology/Oncology, The Cleveland Clinic Foundation. Submitted March 1988; accepted May 1988.

Address reprint requests to J.K.W., Department of Hematology/Oncology, The Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Avenue, Cleveland, Ohio 44195.

CASE REPORTS

Case 1

Patient 1 (father), who was employed as an organist, presented in 1943 at age 58 with dizziness, fainting spells, and epigastric pain. Physical examination revealed a blood pressure of 200/130 mmHg, plethora, and splenomegaly (three fingerbreadths below the costal

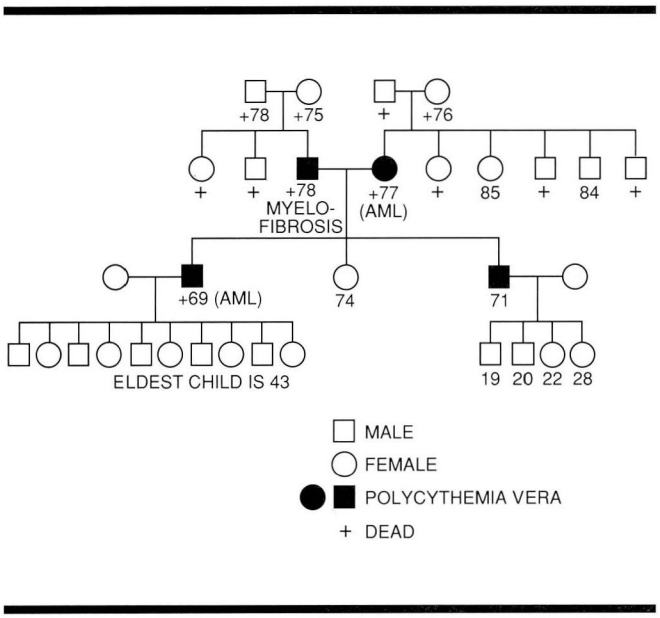

FIGURE 1. Pedigree of our cases of familial polycythemia vera. Current age or age at the time of death is recorded.

margin). RBC count was 10,120,000/μL, hemoglobin 23 g/dL, and hematocrit 78%. The RBC volume was 124 mL/kg. The WBC count was 13,450/μL (80 neutrophils, eight lymphocytes, two eosinophils, two monocytes, two basophils) and the platelet count was normal. Oxygen saturation, P_{50}, leucocyte alkaline phosphatase (LAP) score, and B12 level were not obtained, and hemoglobin electrophoresis was not performed. He had no known cardiopulmonary disease. His father had died of unknown cause at age 78 and his mother had died of kidney disease at age 75. Two siblings were healthy. There was no family history of blood dyscrasias.

He was treated with phlebotomies initially and then a six-month regimen of nitrogen mustard. In 1950, P-32 treatment was started and he received 63 mCi (2.331 GBq) over the next 11 years. He experienced frequent headaches, substernal chest pain, and the onset of Parkinson's disease during this time.

Chlorambucil therapy was started in 1962. This was continued for 10 months, when anemia and thrombocytopenia were discovered. Two months after stopping the chlorambucil, his hemoglobin level was 10.2 g/dL, WBC count 4,600/μL, and platelet count moderately decreased. The peripheral smear revealed oval, teardrop, and bizarre-shaped RBCs, compatible with either a myelodysplastic syndrome or myelofibrosis. The sternal aspirate was hypocellular with no evidence of leukemia. Testosterone was administered. He died of a massive stroke shortly thereafter.

Case 2

Patient 2 (mother), a homemaker, presented in 1938 at age 52 with headaches, fainting episodes, and fatigue. Physical examination revealed a blood pressure of 180/124 mmHg, facial plethora, and hepatosplenomegaly (liver and spleen palpable 3 cm below the costal margins). RBC count was 7,940,000/μL, hematocrit 56%, and hemoglobin 15 g/dL. The RBC volume was 59 mL/kg. The WBC count was 14,400/μL (84 neutrophils, eight lymphocytes, two eosinophils, three monocytes, and three basophils), and the platelet count was normal. Oxygen saturation, P_{50}, LAP score, and B12 level were not obtained, and hemoglobin electrophoresis was not performed. The patient had no demonstrable cardiopulmonary disease. Her father had died of lung disease and her mother had died of a stroke at age 76. Four siblings were healthy. There was no family history of blood dyscrasias.

She was treated with phlebotomies initially. Therapy with P-32 was started in 1950. During the next 10 years, she received over 50 mCi (1.85 GBq) of P-32. She experienced episodes of gout, thrombophlebitis, epistaxis, and pruritus.

By 1962, she had progressive weakness and hepatosplenomegaly. Her hemoglobin level was 8.1 g/dL and the WBC count 17,000/μL with 5% blasts. Findings on bone marrow aspirate were consistent with acute myelogenous leukemia. She was treated with 6-mercaptopurine and prednisone but died in March 1963.

Case 3

Patient 3 (son), an attorney, presented in 1961 at age 52 with bath pruritus and a history of lightheadedness and fatigue. Physical examination revealed a blood pressure of 145/100 mmHg, plethora, a palpable spleen (4 cm below the costal margin) and a palpable liver. RBC count was 7,800,000/μL, hemoglobin 22.8 g/dL, and hematocrit 69%. WBC count was 9,400/μL with a normal differential. Platelets were slightly increased. RBC mass, oxygen saturation, P_{50}, LAP score, and B12 level were not obtained, and hemoglobin electrophoresis was not performed. There was no known cardiovascular disease.

He was treated with phlebotomies and chlorambucil (4–6 mg/day) from 1961 to 1972. In 1972, he was switched to melphalan for unknown reasons. This was discontinued after one year and chlorambucil resumed. Throughout the course of his disease, he had intermittent episodes of fatigue, bath pruritus, and thrombophle-

TABLE 1
SERIAL BLOOD COUNTS ON PATIENT #4 PRIOR TO TREATMENT

	1961	1977	1978	1980	1981	1983
RBC (million/μL)	4.8	5.27	5.37	5.80	6.54	7.70
Hemoglobin (g/dL)	14.6	15.2	17.2	17.4	19.4	20.7
WBC (/μL)	6,000	7,200	8,000	11,100	10,700	11,200
Platelets (/μL)	"normal"	468,000	–	–	–	784,000

bitis. An intravenous pyelogram obtained in 1972 because of urinary urgency and frequency revealed mild right ureteropelvic junction obstruction.

In 1976, he complained of marked fatigue and was found to be anemic and thrombocytopenic. The WBC count was 10,200/μL with 70% blasts. He was treated unsuccessfully with vincristine, prednisone, and 6-mercaptopurine and died in 1977.

Case 4

Patient 4 (son), an accountant, presented in 1983 at age 70 with fatigue and weakness, occasional lightheadedness, and tinnitus. He had a history of an inferior myocardial infarction and two episodes of amaurosis fugax of the right eye in 1977. Carotid angiograms were normal and coronary angiography revealed total occlusion of the proximal right coronary artery. Physical examination was remarkable for a blood pressure of 180/100 mmHg and plethora. There was no splenomegaly. Because both parents and a brother had polycythemia vera, blood counts had been performed frequently during the preceding six years. These revealed gradually increasing hemoglobin levels and WBC and platelet counts (*Table 1*). The RBC mass was 69.8 mL/kg, LAP score 82, and serum B12 level 410 pg/mL. The P_{50} was normal at 26.5 mmHg. Oxygen saturation was 91.3% with a PO_2 of 68 mmHg. Full pulmonary function tests were normal except for elevated DLCO (37 mmHg, normal 21.9 mmHg). Chest radiographs revealed mild enlargement of the cardiac silhouette and a vague, diffuse interstitial infiltrate unchanged from five years previously. The patient had no cardiopulmonary symptoms and jogged 4 miles/day (6.4 km/day). He had a 40 pack-year smoking history, but had quit smoking 15 years previously. The serum erythropoietin level was 150 milli-immunochemical units (normal, 25–75 milli-immunochemical units) before any phlebotomies. He had four healthy children.

He has been treated with phlebotomy to a hematocrit of less than 45%. He continues to complain of intermittent fatigue and pruritus and has a persistent thrombocytosis of greater than 1,000,000/μL.

DISCUSSION

Familial polycythemia may be either primary (polycythemia vera) or secondary. Secondary causes include mutant hemoglobins with increased oxygen affinity, decreased erythrocyte diphosphoglycerate, abnormal erythropoietin production and/or regulation, congenital cardiopulmonary disease, methemoglobinemia, and other mechanisms.[10,18] Most previously reported cases of familial polycythemia vera fall into the secondary category and are well reviewed by Adamson.[10]

Familial cases of primary polycythemia (polycythemia vera) are distinctly unusual. Fourteen families have been reported (*Table 2*).[1–9,19] In eight of these families, adequate laboratory data are available to meet the strict diagnostic criteria of the Polycythemia Vera Study Group.[18] In five families, one or more laboratory values are lacking so that the strict Polycythemia Vera Study Group criteria cannot be fulfilled. However, in all five cases, splenomegaly plus an elevated leukocyte or platelet count are recorded, making a secondary form of polycythemia unlikely. In one family, that reported by Erf,[19] insufficient information is available to diagnose familial polycythemia vera. Thus, 13 familial cases of polycythemia vera are adequately documented. In only one family are more than two members affected.[3] In four families, the affected members are siblings (nontwin),[1–3,8] and in three families affected members are identical twins.[5–7] In the remaining six families, the affected members are one parent-one child combinations.

The family we report is unique in that four members are affected (mother, father, and two sons) and a large pool of offspring in the third generation is available for continued follow-up. None of the 14 offspring in the third generation has demonstrated signs of polycythemia vera at this time; however, the oldest of them is currently only in his 40s.

Our patient 4 meets the Polycythemia Vera Study Group diagnostic criteria[18] except for an oxygen saturation of 91.3% instead of 92%. He has no respiratory symptoms and full pulmonary function tests are normal except for elevated DLCO. Vague interstitial infiltrates

TABLE 2
SUMMARY DATA ON 13 KINDREDS WITH FAMILIAL POLYCYTHEMIA VERA

Author	Pt. no.	Age at diagnosis (yr)	Relationship	RBC volume (mL/kg)	O_2 Sat.	Splenomegaly	Platelet count (/μL)	WBC (/μL)	LAP score	B_{12} (pg/mL)	Chromosomes	Treatment	Outcome
Lawrence and Goetsch[1]	2	61	brother		90%	+	450,000	46,000				phleb, phenylhydrazine, P-32	Died age 74 of uremia
	3	48	sister		97%	+	1,329,000	27,900				phleb, P-32	Alive 13 years later
Levin et al[2]	1	68	brother	62.5	"normal"	+	293,000	13,800	157		46 Ph' +	phleb, P-32	Alive
	2	44	brother			+	951,000	22,250	189		46 Ph' +	phleb, P-32	Alive
Manoharan and Garson[3]	1	48	sister		94%	+	366,000	37,000	185	2,050	abnormal	phleb, P-32	Myelofibrosis 12 years later
	2	68	sister	59	92%	+	270,000	12,000	184			phleb, P-32	Alive 11 years later
	3	60	sister	44.7	93%	+	340,000	13,000	50	1,050	abnormal	phleb, P-32	Myelofibrosis 5 years later
Ratnoff and Gress[4]	1	53	father			+	294,000	17,800			normal	phleb	Myelofibrosis 10 years later
	2	44	son	72.7	"normal"	+	302,000–616,000	17,500	271	776		phleb	Alive 2 years later
Fairrie et al[5]	1	49	monozygotic twin			+	319,000	37,200				P-32, splenic radiation	Died of mesenteric thrombosis 14 years later
	2	75	monozygotic twin	48		+	235,000	21,000	225		normal	phleb	Alive
Burnside et al[6]	1	64	monozygotic twin	96		+	"raised"	"raised"				phleb, P-32	Alive 6 years later
	2	67	monozygotic twin	55		+	"raised"	"normal"				phleb, P-32	Alive 3 years later
Friedland et al[7]	1	55	monozygotic twin	43	98%	+	500,000	11,000	183	749	normal	phleb	Alive 4 years later
	2	56	monozygotic twin	41	96%	+	730,000	9,000	242	1,352	normal	phleb	Alive 3 years later
Waddell et al[8]	1	26	brother	3,249 mL	"normal"	+	258,000–545,000	10,300–13,600	107	>1,600	normal	phleb, P-32	Alive 26 years later
	2	41	brother	3,199 mL	>92%	+	333,000–720,000	10,300–18,500	101	>2,000	normal	phleb	Alive 4 years later
Brubaker et al[9]	1	45	daughter	40	92%	+	616,000	12,300	138	460		phleb, chlorambucil	Alive 10 years later
		59	mother	52	99%	+	407,000	17,900	368			P-32, busulfan, phenylalanine mustard	Died of acute leukemia 12 years later
	2	65	son	74.8	93.6%	+	285,000	14,900	182	520		phleb	Alive 8 years later
		60	father	"elevated"		+	320,000	9,000				P-32, phenylhydrazine	Alive 20 years later
	3	49	son	50.6	97%	+	725,000	8,700	58	705		phleb	Alive 2 years later
		51	father	64		+	310,000	22,400				P-32, Fowler's solution	Died of acute leukemia 20 years later
	4	67	son	45	96%	+	390,000	4,400	12	1,285		phleb	Alive 2 years later
		79	mother	"marked increase"		+	382,000	7,800	242			P-32	Myelofibrosis 20 years later
	5	58	son	59.8	98%	+	418,000	18,000	224			P-32	Alive 10 years later
		82	mother	40.8		+	"elevated"	12,900				phleb	Alive 9 years later
Miller	1	58	father	124		+	"normal"	13,450				phleb, HN_2, P-32, chlorambucil	Myelofibrosis and fatal stroke 20 years later
	2	52	mother	59		+	"normal"	14,400				phleb, P32	Died of acute leukemia 25 years later
	3	52	son			+	"slightly increased"	9,400				phleb, chlorambucil, melphalan	Died of acute leukemia 15 years later
	4	70	son	69.8	91.3%	0	784,000–1,130,000	11,200–13,900	82	410		phleb	Alive 1.5 years later

phleb = phlebotomy.

of unknown etiology are present on chest radiographs, but have been unchanged for five years. His symptoms and clinical course are classic, however, and he had a normal P_{50}, ruling out a mutant hemoglobin with increased oxygen affinity as a cause for his polycythemia. He did, however, have an unexplained mildly elevated serum erythropoietin assay prior to treatment. Erythropoietin levels were not reported in any other cases of familial polycythemia vera. There has been no evidence of renal disease or occult neoplasm during the 18 months since his diagnosis.

It is highly unlikely that abnormal production and/or regulation of erythropoietin is responsible for this family's polycythemia because splenomegaly and elevated neutrophil and/or platelet count were present in the other members, as was transformation to either acute nonlymphocytic leukemia or myelofibrosis. None of these findings would be expected with secondary causes of familial polycythemia.

The other three members of our family did not meet the strict Polycythemia Vera Study Group diagnostic criteria because they were diagnosed at a time when oxygen saturation, LAP score, and B12 levels were not routinely measured. Their classic clinical symptoms, splenomegaly, leukocytosis and/or thrombocytosis, and their progression to myelofibrosis or acute nonlymphocytic leukemia strongly support the diagnosis of polycythemia vera.

The age at diagnosis (mean 57 years, median 58 years, range 26–82 years) for the previously reported familial cases plus our four cases is similar to that for nonfamilial polycythemia vera (mean 60 years, range 20–85 years).[18] Likewise, a male predominance is found in familial cases as well as nonfamilial ones; the male/female ratio for familial cases was 1.8/1, while that of nonfamilial ones was 1.2/1.[18]

In the familial cases, the mean RBC volume was 60 mL/kg, slightly higher than the 49 mL/kg seen in nonfamilial cases studied by the Polycythemia Vera Study Group.[18] Oxygen saturation was reported in 14 of 31 familial cases and found to be ≥ 92% in 12 cases. Splenomegaly was present in 30/31 familial cases (97%) whereas it is found in only 70% of nonfamilial cases.[18] A platelet count greater than 400,000/μL or "elevated" was reported in 17/31 (55%) familial cases and 43% of nonfamilial cases.[18] WBC count greater than 12,000/μL or "raised" was reported in 22/31 (71%) familial cases and 63% of nonfamilial ones.[18] LAP score was reported in 19 of the familial cases and was elevated (greater than 100) in 15 (79%). Seventy percent of patients studied by the Polycythemia Vera Study Group had an elevated LAP score.[18] Thus familial cases have a similar age of onset, male predominance, and incidence of elevated WBC count, platelets, and LAP scores. They have a slightly higher mean RBC volume at diagnosis and an increased incidence of splenomegaly.

Symptoms reported in patients with familial polycythemia vera are similar to those in nonfamilial cases and consist mainly of pruritus, headaches, weakness, and dizziness.

It has been reported that polycythemia vera is more frequent among Jews of European extraction[13] and less frequent in blacks than whites.[12] For most familial cases, race and religion have not been specified; however, the family reported by Ratnoff and Gress[4] was Jewish and that reported by Waddell et al[8] was black. The family we report was white, of Bavarian-German ancestry, and Roman Catholic.

Consanguinity was not mentioned in any of the previously reported familial cases. In the family reported here, there was no known blood relationship between the affected mother and father.

Of the 31 reported patients with familial polycythemia vera, five (16%) have disease that has progressed to myelofibrosis (5, 10, 12, 20, and 20 years after diagnosis) and four (13%) have developed acute leukemia (12, 15, 20, and 25 years after diagnosis). The actual incidence of acute leukemia or myelofibrosis in familial polycythemia vera cannot be determined as yet since many of the patients are still alive and have had limited follow-up time since diagnosis.

Cytogenic studies in patients with polycythemia vera reveal a nonrandom pattern of abnormalities that most frequently involves chromosomes 1, 8, 9, and 20.[14] The incidence of abnormal karyotypes in untreated patients is 13%–26%, and in treated patients it jumps to 38%–44%.[14–16] Abnormal karyotypes present early in the disease do not predict eventual leukemic transformation, but a change in karyotype during the course of disease may herald leukemic transformation.[14]

Of 13 reported kindreds with familial polycythemia vera, chromosome studies were done in six.[2–5,7,8] Four of these families had normal karyotypes[4,5,7,8] and two revealed abnormalities.[2,3] The two brothers reported by Levin et al[2] were Philadelphia-chromosome positive. One brother was studied prior to treatment with P-32 and the other after. Two of the sisters with familial polycythemia vera reported by Manoharan and Garson[3] were studied cytogenetically after treatment with P-32. On one occasion, they each had normal karyotypes and, at other times, one sister demonstrated 46,XX,–E,+Er and 47,XX,+C while the other sister demonstrated 46,XX,–A,+mar. In this limited group of fa-

milial polycythemia vera patients, the incidence of cytogenetic abnormalities was not higher than that in polycythemia vera patients in general, and no consistent abnormalities were found.

Exploring the etiology of familial aggregations of polycythemia vera, one must consider environmental as well as genetic factors. Scattered case reports of polycythemia in patients exposed to various toxic agents are found in the literature.[12] In most instances, the patients demonstrated a polycythemia, but not primary polycythemia vera. A few cases of true polycythemia vera associated with benzene exposure have been reported, and benzene has also been implicated in the etiology of other myeloproliferative disorders.[12] Ratnoff and Gress[4] reported a familial occurrence of polycythemia vera in a father and son exposed to organic solvents. Friedland et al[7] reported identical twins with polycythemia vera who also had organic solvent exposure. Other reports of familial polycythemia vera do not mention any associated environmental agents. No unusual environmental exposure could be documented in the family we studied. They hailed from a small town in Ohio, and the patients worked as a musician, housewife, attorney, and accountant, with no known industrial exposure. The incidence of familial erythrocytosis is not of a frequency to warrant routinely testing the family members of affected individuals unless they exhibit compatible symptoms or signs of absolute erythrocytosis.

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