Medical Case Studies Vol. 3(2), pp. 9-11, May 2012
Available online at http://www.academicjournals.org/MCS
DOI: 10.5897/MCS11.031
ISSN 2141-6532 ©2012 Academic Journals

Case Report

Autosomal dominant inheritance with variable penetrance in primary familial and congenital polycythemia: A family tree

JAIN P. K., SIDDIQUI M. Z., GABA R.*, SRIVASTAVA G., JAISWAL P., SRIVASTAVA S. and SHUKLA A.

Department of Medicine, MLB Medical College, Jhansi (U.P.) - 284128, India.

Accepted 5 January, 2012

Primary familial and congenital polycythemia is a rare congenital disorder with only one case ever reported from Indian Subcontinent. Here, we are reporting an entire family inflicted with primary familial and congenital polycythemia, first ever of its kind from Indian subcontinent. We are of firm belief that our report would create awareness among medical fraternity in India about this under reported disorder.

Key words: Primary familial and congenital polycythemia, erythropoietin, autosomal dominant, variable penetrance, sporadic, erythropoietin receptor, Chuvash polycythemia.

INTRODUCTION

Primary familial and congenital polycythemia (PFCP) is the only recognized type of primary familial polycythemia. It is characterized by an autosomal dominant mode of inheritance, and less frequently, by the occurrence of sporadic cases. This is in contrast with Chuvash polycythemia where the inheritance is autosomal recessive. The clinical features of primary familial and congenital polycythemia include the absence of predisposition to the development of acute leukaemia or other myeloproliferative disorders, absence of splenomegaly, normal white blood cell and platelet counts, low plasma erythropoietin (Epo) levels, normal haemoglobin-oxygen dissociation curve (indicated by a normal P50) and hypersensitivity of erythroid progenitors to exogenous erythropoietin *in vitro*. Primary familial and congenital polycythemia is generally thought to be a benign condition, but it has been reported to be associated with a predisposition to cardiovascular problems (Queisser et al., 1988; Prchal et al., 1995) such as hypertension, coronary artery disease, and cerebrovascular events though these events are not clearly related to an elevated haematocrit.

Characteristic laboratory findings are: (i) An increased red blood cell mass without increases in leukocyte or platelet counts; (ii) Normal vitamin B12 levels; (iii) Normal haemoglobin-oxygen dissociation; (iv) Low serum Epo levels; and (v) *In vitro* hypersensitivity of erythroid progenitors to Epo (Prchal et al., 1985; Juvonen et al., 1991).

Primary familial and congenital polycythemia is caused by a mutation in the Erythropoietin receptor resulting in hypersensitivity to Epo. Several mutations have been identified in the Epo receptor (EPOR*)* gene; however, EPOR mutations have not been identified in all primary familial and congenital polycythemia cases. Most identified EPOR mutations cause truncation of the c-terminal cytoplasmic receptor domain of the receptor. These truncated receptors have heightened sensitivity to circulating Epo due to a lack of negative feedback regulation. To date, 12 mutations of EPOR have been described. Nine out of the 12 result in truncation of the EPOR cytoplasmic carboxyl terminal and are the only mutations convincingly associated with PFCP. Such truncations lead to a loss in the negative regulator domain

*Corresponding author. E-mail: ripu_2cool@yahoo.com. Tel: +919695980274. Fax: +91-510-2321937.

Abbreviation: PFCP, Primary familial and congenital polycythemia; **Epo,** erythropoietin, **EPOR,** Epo receptor.

of the EPOR, associated with SHP-1, and reinforce the crucial importance of retained positive regulatory domains associated with the JAK2/STAT5 proteins.

Chuvash polycythemia is due to an abnormality in the oxygen-sensing pathway caused by inheritance of mutations in the VHL gene. Chuvash polycythemia needs to be considered, particularly, those with an increased or inappropriately normal serum Epo concentration for the elevated hematocrit level. Chuvash polycythemia is a unique VHL syndrome characterized by homozygous germ line mutation of VHL, increased mortality because of cerebral vascular events and peripheral thrombosis, distinct vascular abnormalities, intact hypoxia sensing despite increased systemic expression in normoxia of a broad range of HIF-1–regulated genes, and absence of a predisposition to develop tumors or malignancy (Gordeuk et al., 2004).

Congenital polycythemia due to altered oxygen sensing but without mutation of VHL is seen in more than one-half of patients with congenital polycythemias with normal or elevated Epo levels. Lesions in genes linked to oxygen-dependent gene regulation and their interacting proteins are leading candidates for mutation screening in polycythemic patients with normal or elevated Epo without VHL mutations.

Cyanotic congenital heart disease is an important cause of polycythemia in young children worldwide. Inherited conditions that increase the affinity of hemoglobin for oxygen are important but rare causes of congenital polycythemia. These conditions include high affinity haemoglobin disorders (Wajcman and Galacteros, 2005) deficiency of 2, 3 DPG, and methemoglobinemia due to haemoglobin M or to deficiency of cytochrome b5 reductase.

CASE REPORT

Mr. Raju, a 45 year old male was admitted in Department of Medicine, Maharani Laxmi Bai (MLB) Government Medical College, Jhansi, India as a case of uncontrolled hypertension. Patient was a known case of systemic hypertension for past 12 years. Patient was on clonidine, furosemide and nifedipine at the time of presentation. On examination there was no organomegaly, no cutaneous manifestations and no apparent signs of any systemic involvement. During routine investigations patient's hematocrit and hemoglobin were detected to be markedly high whereas platelet and leucocyte counts were within normal limit. Patient's erythropoietin level was 4.29 mIU/ml at the time of presentation. Serum Epo level was 4.71 mIU/ml after phlebotomy. As patient's erythropoietin level was low (Gordeuk et al., 2005) the disorder was primary. And as patient had no evidence of splenomegaly and his platelet and leucocyte counts were within normal limits, a provisional diagnosis of primary familial and congenital polycythemia was made.

Also patient's hemoglobin electrophoresis was normal ruling out the possibility of abnormal haemoglobin variant which in any case is a secondary cause of polycythemia. Real time PCR analysis was carried out which failed to detect JAK2 mutation. Patient's relatives were screened for polycythemia and two of his brothers, one of his sister, his son and his maternal cousin were also diagnosed with polycythemia. From the analysis of the pedigree tree, it's clear that the inheritance pattern in the above reported family is autosomal dominant with variable penetrance. Our setup is peripheral and we work under great financial constraints and the facilities for further genetic testing are not available in our setup.

Patient's brother not only suffered from primary familial and congenital polycythemia but also suffered from coronary artery disease.

DISCUSSION

Gordeuk et al. (2005) described an approach to a patient of polycythemia which was the cornerstone of our study. The erythropoietin levels were normal in our patient, thus, we evaluated the patient for splenomegaly, leucocytosis, thrombocytosis all which were absent. Hence, a probable diagnosis of primary familial and congenital polycythemia was made. On screening the patient's first degree relatives two of his brothers, one of his sister, his son and his maternal cousin were also diagnosed with polycythemia.

Dar et al. (2009) reported the first case of Primary familial and congenital polycythemia from Indian subcontinent. We are reporting the second case of primary familial and congenital polycythemia from Indian subcontinent and also presenting the first ever genetic tree of its kind from Indian subcontinent.

Jedlickova et al. (2003) confirmed by linkage analysis that primary familial and congenital polycythemia was not linked to the Epo and EPOR genes in the family studied. They identified a region in 7q22.1 to 7q22.2 with a suggestive LOD score of 1.84, which according to their data was the most likely location of a candidate region responsible for primary familial and congenital polycythemia in the earlier mentioned family.

Ernanuel et al. (1992) concluded that the mechanisms for the erythrocytosis in familial and congenital polycythemia may not involve the EPO-receptor and, therefore, may result from alterations of post receptor responses. In a recent study, mutations of the *EPOR* were found in only 12% of subjects with PFCP, suggesting that in a majority of PFCP families, mutations in genes other than EPOR result in defective Epo signalling and accumulation of erythrocytes (Kralovics and Prchal, 2001; Jedlickova et al., 2003).

Primary familial and congenital polycythemia predisposes patients to severe cardiovascular problems

(Queisser et al., 1988; Prchal et al., 1995). An increased incidence of cardiovascular disease was observed in affected members of primary familial and congenital polycythemia (Sokol et al., 2001).

Conclusions

Primary familial and congenital polycythemia is a rare congenital condition whose inheritance pattern is autosomal dominant. The family reported in our study depicts autosomal dominant inheritance with incomplete penetrance. Our study also emphasizes on association of cardiovascular diseases with primary familial and congenital polycythemia.

ACKNOWLEDGEMENTS

We acknowledge Professor Dr. Ganesh Kumar, Principal and Dean, MLB Medical College, Jhansi, UP-India for helping us in publication of this article and providing adequate facilities for working on this study. The authors are highly thankful to the Residents of Postgraduate Department of Medicine, MLB Medical College, Jhansi, UP-India, for their ever tiring hard work on this study.

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