Homozygous haemoglobin E in association with hereditary ovalocytosis

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Summary

Hereditary stomatocytic ovalocytosis and haemoglobin E are two genes present in 3–5% of Malays. This is a report of a 22 year old Malay college student with homozygous haemoglobin E and hereditary stomatocytic ovalocytosis where the clinical effects seen were the result of the summation of these genes: he was asymptomatic, presenting with moderate jaundice, moderate hepatosplenomegaly, and a mild haemolytic anaemia.

Key words: Homozygous haemoglobin E, hereditary stomatocytic ovalocytosis, haemolytic anaemia.

Introduction

The genetic relationship among the inherited abnormalities of the red blood cells is dependent upon the careful study of certain pedigrees. Up to the present time, only a few instances of the combination of hereditary ovalocytosis and haemoglobin E have been described.[1]

Hereditary ovalocytosis represents a heterogenous group of disorders which differ in clinical expression, red cell morphology and molecular pathology. The abnormality is present in 5.1% of Malays, who are asymptomatic showing no overt haemolysis or splenomegaly. They are usually picked up as an incidental finding from a routine blood film examination. Ektacytometric studies of the peripheral blood show the red cells are markedly rigid indicating a skeletal protein defect which has yet to be identified.[2]

Haemoglobin E ($\alpha_2\beta_2 26$ Glu → Lys) is present in 3–5% of Malays. There is no evidence that individuals with haemoglobin E trait have any significant haemolysis. The reticulocyte counts are normal and there is no anaemia or splenomegaly. Similarly haemoglobin E disease seems to be an extremely mild disorder with minimal anaemia and the spleen being palpable occasionally. Although the red cells are small and poorly haemoglobinised the reticulocyte count is consistently normal and apart from the presence of target cells, mild hypochromia, it is quite clear that there is not a significant haemolytic component.[3]

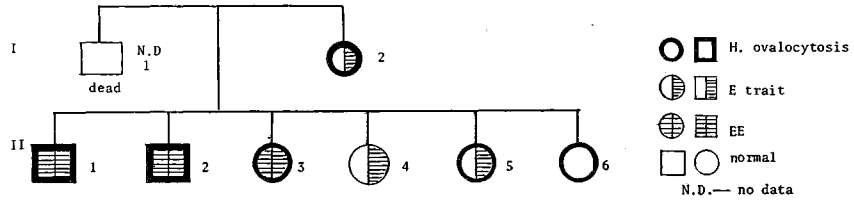
The following is the report of a Malay family in which a haemoglobin E gene occurred in combination with a gene for hereditary ovalocytosis. Haematologic and genetic studies in this

family permit concluding that the genes are not closely linked and inherited independently from each other. In addition there is suggestive evidence that the clinical effects of both genes are summated when they are both present in the same individual.

Case report

The family is of Malay extraction and their pedigree is presented in Figure 1. The propositus (Figure 1 – 11.2) is a 22 year old college student who was referred to the haematology clinic by an Optometrist who had observed jaundice. Prior to this he had been in good health and had no history of blood transfusions or hospital admissions. The physical examination revealed a young adult of normal height and weight, no thalassaemic facies, moderate jaundice, and moderate hepatosplenomegaly (Liver – 4 cm; Spleen – 4 cm). Examination of the peripheral blood showed marked stomatocytic ovalocytes (>90%), mild hypochromia, moderate anisopoikilocytosis and some target cells (Figure 2). The electron scan of the red cells showed some cells with pits (Figure 3). The reticulocyte count was 1.8%, and the serum ferritin level 100 ng/ml. A blood specimen was sent to the Department of Cell and Molecular Biology, Medical College of Georgia, United States of America for structural analysis of the haemoglobin and DNA studies. The α gene status by restriction endonuclease mapping showed normal α gene maps. Haemoglobin electrophoresis performed on cellulose acetate Tris EDTA borate pH 8.6 showed the presence of haemoglobin E and no Haemoglobin A. Globin treated with 8 M urea and mercaptoethanol on cellulose acetate pH 6.0 showed no β^A formation and the presence of α, β^E, δ and γ chains. The α/β^E globin synthesis ratio was 2.0 and the bone marrow demonstrated normoblastic erythroid hyperplasia. The dichloroisopropanol (DCIP) test was positive and the red survival using ^{51}Cr was 13.2 days (normal T 1/2 Cr = 33 days). The serum bilirubin was 119 mmol/L (normal < 20 mmol/L) and the liver enzymes alanine transaminases and the alkaline phosphatase were within normal limits.

Figure 1.0 Pedigree of Family MS



Code Designation	Age	Sex	Hb	RBC	HCT	MCV	MCH	MCHC	HbE	HbF	S.B	Diagnosis
I.1	68	M	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	Dead
I.2	58	F	13.9	4.8	0.41	85.2	28.9	33.9	31.0	0.4	10	AE/HO
II.1	14	M	10.4	4.4	0.31	71.8	23.6	32.9	80.8	3.9	31	EE/HO
II.2*	22	M	12.4	5.9	0.42	71.7	20.7	28.9	91.1	1.2	119	EE/HO
II.3	20	F	9.8	4.5	0.31	68.1	21.7	31.9	87.0	1 0	91	EE/HO
II.4	26	F	12.3	4.7	0.37	79.0	25.8	32.6	30.0	0.3	12	AE
II.5	32	F	12.8	4.2	0.37	89.0	30.7	34.5	30.4	0.3	12	AE/HO
II.6	36	F	12.8	3.8	0.35	93.4	33.6	36.6	3.0	0.2	11	AA/HO

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Hb = gm/dl; RBC = 10x /L; HCT %; MCV = fl; MCH = pg; MCHC = %; HbE = %;
HbF = %; S.B = bilirubin mmol/L; M = Male; F = Female

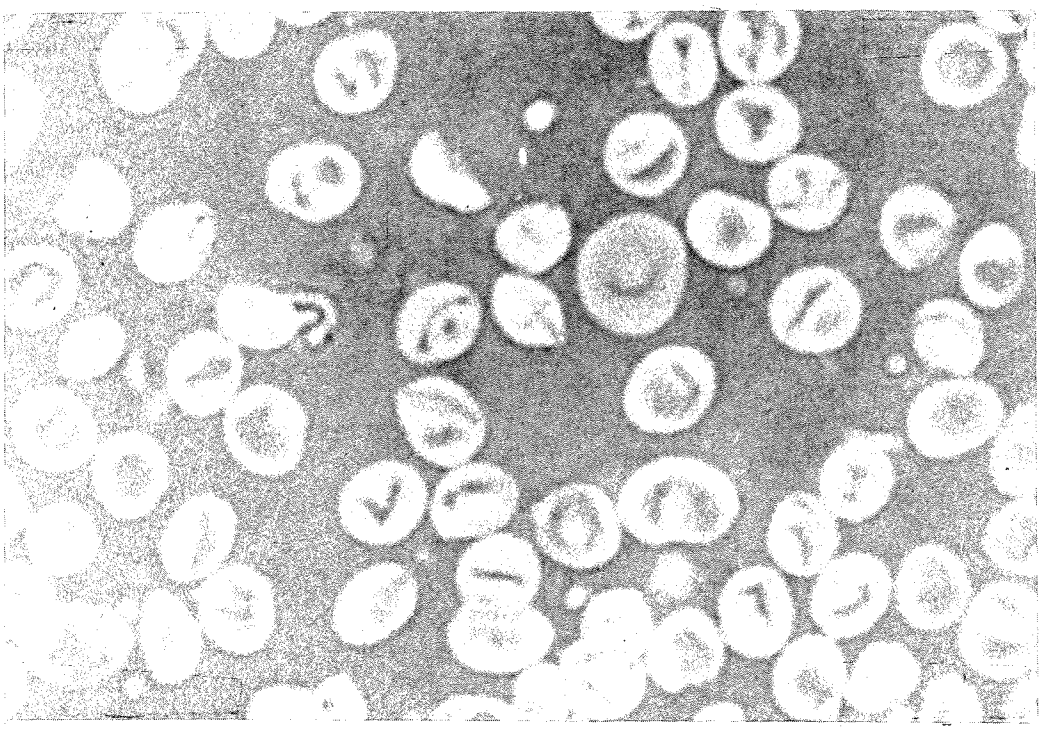

Fig. 2 Peripheral blood of a case with hereditary ovalocytosis and homozygous haemoglobin E

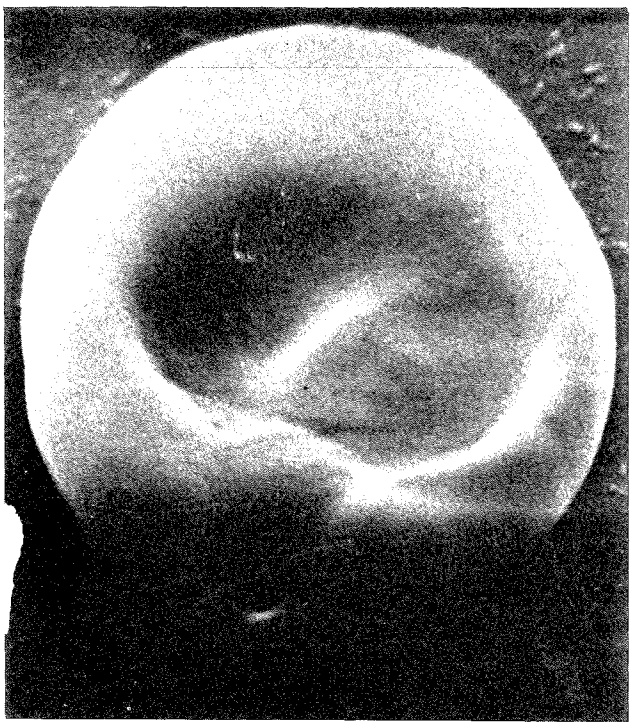

Fig. 3 Electron scan of a cell with stomatocytic ovalocytosis

Family history revealed that the father (Figure 1 – 1.1) died at the age of 68 years followeing a heart attack. No haematological data was available of him. All siblings (Figure 1 – 11.1–6) were in good health, asymptomatic, and prior to the family study did not know of their inheritance of the genes of haemoglobin E and hereditary stomatocytic ovalocytosis. The siblings (Figure 1 – 11.1 and 11.3) had similar haematological and clinical findings as the propositus. The siblings with a trait of haemoglobin E (11.4) and the double heterozygote (traits of haemoglobin E and hereditary ovalocytosis – 11.5), had normal haemoglobin and serum bilirubin levels, and no hepatosplenomegaly.

Discussion

Data collected in the Malayan aborigines by Lie Injo[1] have described hereditary ovalocytosis in association with heterozygous haemoglobin E as not having produced clinical or haematological symptoms. The limited investigations and the data presented did not permit conclusions regarding the relationship of homozygous haemoglobin E and hereditary ovalocytosis.

The clinical effects of the genes of hereditary stomatocytic ovalocytosis and homozygous haemoglobin E are summated in 11.1, 11.2 and 11.3 as seen by their raised bilirubin levels, anaemia (mild to moderate), reduced red cell survival times and presence of moderate hepatosplenomegaly. Stomatocytic ovalocytes have decreased deformability[2] and this results in their reduced ability to navigate narrow capillary vessels and the splenic sinusoids. The constant bombardment of the reticuloendothelial elements by the abnormal red cells (with excess α chains) where the cells may remain trapped as a consequence of decreased deformability or have inclusions removed result in the enlargement of the liver and the spleen. The removal of the excess α chains results in the abnormalities as seen in the electron scan of the red cells.[4]

This case report highlights the clinical effects that result from the association of homozygous haemoglobin E and hereditary stomatocytic ovalocytosis where a partially compensated haemolytic state, moderate jaundice, enlarged liver and spleen are seen although the affected persons are asymptomatic.

References

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