Southeast Asian Ovalocytosis in an African-American Family

To The Editor:

A form of hereditary elliptocytosis (HE) characterized by extremely rigid erythrocytes and resistance to invasion by malarial parasite is found in high frequency in several Southeast Asian countries, reaching an incidence of 30% in certain ethnic groups.[1-5] The first characterization of rigid properties of these HE erythrocytes was in patients from Malaysia (Melanesian ovalocytosis),[1] but the same disorder has been described in individuals from Papua New Guinea, the Philippines, and Indonesia and is now given the name Southeast Asian ovalocytosis (SAO).[4,5] The prevalence of SAO in the Indian subcontinent and Africa is unknown, but there is at least one report of SAO in a Mauritian of Indian descent.[6] The molecular defect of SAO erythrocyte is now well known to be the deletion of amino acids 400-408 of band 3, the anion exchange protein, which lie at the interface between the N-terminal cytoplasmic domain and

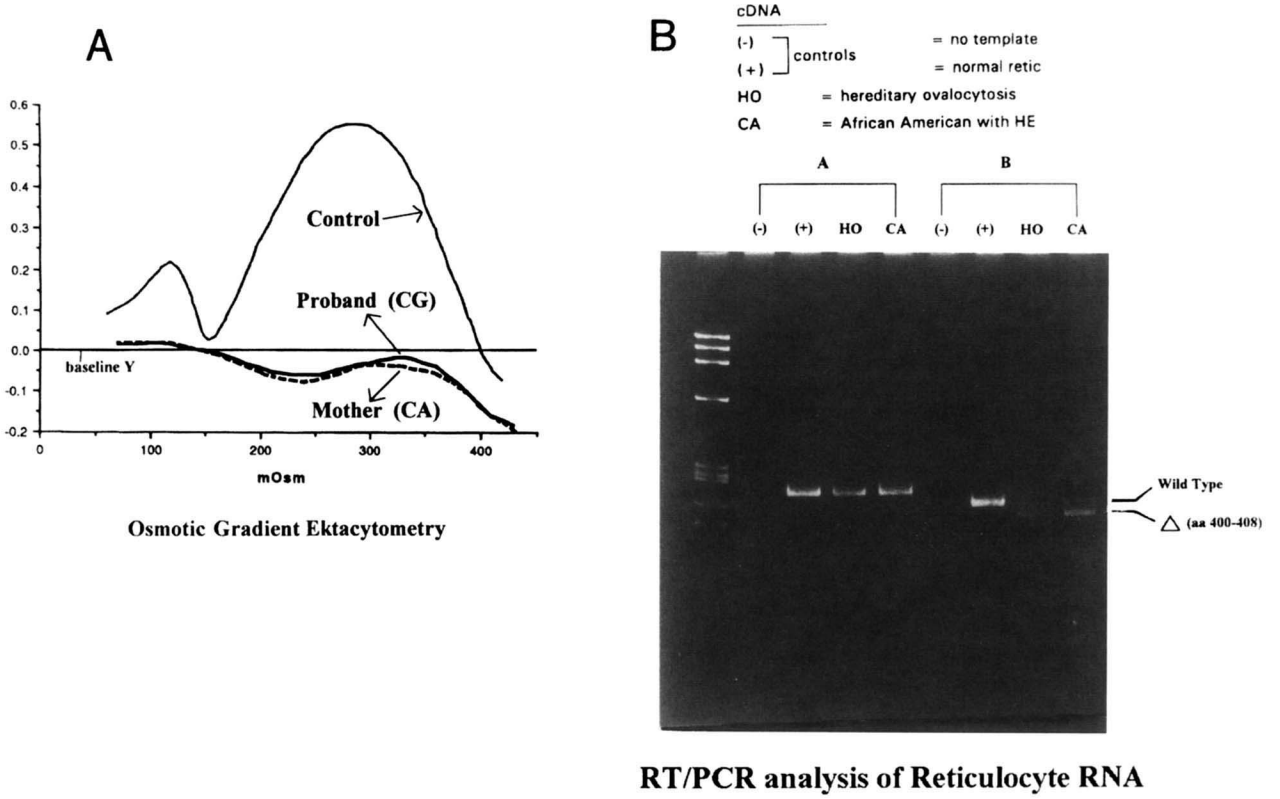

Fig 1. (A) Osmotic gradient ektacytometry. Red blood cell deformability was measured in the ektacytometer at various osmolalities as described by Clark et al.[15] (B) RT/PCR analysis of reticulocyte RNA. Total RNA was extracted from whole blood and was amplified with band 3 primers (A) spanning nucleotides 464-723 of the cytoplasmic domain and (B) spanning nucleotides 1104-1334, which contain the deletion characteristic of SAO.

the point at which the polypeptide chain enters the membrane.[6-8] Band 3 also has a common polymorphism, the so-called Memphis-1 variant, in which the point mutation lys56 → glu produces a protein with slower electrophoretic mobility and an abnormal chymotryptic fragment.[9,10] All of the cases of SAO to date have been associated with the Memphis-1 polymorphism. The molecular defect in the case of the Mauritian Indian in Tanner et al[6] was identical to the defect noted in SAO cases from Papua New Guinea.

The polymorphic variant, band 3 Memphis 1, is found in 6% to 7% of random human blood samples and is common in all populations but is present at higher frequency in American Indian and African-American populations.[11,12] Despite this high frequency of Memphis 1 variant, HE with characteristics of SAO has not been described to date in African-Americans. Rather, the HE in African-Americans (and in North Africans) is often associated with an increased membrane fragility and is caused by point mutations involving the dimer-dimer association site in the α-spectrin molecule.[13]

We now describe an African-American family in which the proband and her mother had the characteristic stomatocytic elliptocytes that were virtually nondeformable as measured by osmotic gradient ektacytometry (Fig 1A). On sodium dodecyl sulfate-polyacrylamide gel electrophoresis, the band 3 protein has a slower mobility than normal and chymotryptic digestion of band 3 protein yielded the two fragments consistent with the presence of the Memphis 1 heterozygosity (data not shown). Anion exchange activity was reduced to 51% of normal in the mother of the proband, which was also consistent with earlier findings with SAO.[14] Reverse transcriptase/polymerase chain reaction (RT/PCR) analysis of reticulocyte mRNA (performed in Dr Mohandas Narla's laboratory) using band 3-specific primers that span the deletion in SAO gave the normal 362-bp band 3 product as well as the smaller 355-bp product containing the 27-bp deletion corresponding to the deletion of 8 amino acids in the peptide chain characteristic of the SAO band 3 protein (Fig 1B). We believe this to be the first example of SAO like HE in Sub-Saharan Africans (to be distinguished from North Africans) and the first such case we have seen among 23 consecutive HE cases in African-Americans we have studied, all of whom had the more common abnormalities involving the α T1 spectrin variants.

ACKNOWLEDGMENT

Supported by the Georgie Ginopolis Fund and the Detroit Comprehensive Sickle Cell Center National Institutes of Health Grant No. HL-16008. The authors thank Julie Nucci for secretarial assistance in preparing this manuscript.

Yaddanapudi Ravindranath
Gerard Goyette Jr
Robert M. Johnson
Department of Pediatrics and Biochemistry
Wayne State University School of Medicine
Children's Hospital of Michigan
Detroit, MI

REFERENCES

1. Lie-Injo LE: Hereditary ovalocytosis and hemoglobin E-ovalocytosis in Malayan aborigines. Nature 208:1329, 1965

2. Mohandas N, Lie-Injo LE, Friedman M, Mak JW: Rigid membranes of Malayan ovalocytes: A likely genetic barrier against malaria. Blood 63:1385, 1984

3. Kidson C, Lamont G, Saul A, Nurse GT: Ovalocytic erythrocytes from Melanesians are resistant to invasion by malaria parasites in culture. Proc Natl Acad Sci USA 78:5829, 1981

4. Saul A, Lamont G, Sawyer WH, Kidson C: Decreased membrane deformability in Melanesian ovalocytes from Papua New Guinea. J Cell Biol 98:1348, 1984

5. Liu SC, Zhai S, Palek J, Golan DE, Amato D, Hassan K, Nurse GT, Babona D, Coetzer T, Jarolim P, Zaik M, Borwein S: Molecular defect of the band 3 protein in southeast Asian ovalocytosis. N Engl J Med 323:1530, 1990

6. Tanner MJ, Bruce L, Martin PG, Rearden DM, Jones GL: Melanesian hereditary ovalocytes have a deletion in red cell band 3 (letter). Blood 78:2785, 1991

7. Tanner MJA: Molecular and cellular biology of the erythrocyte anion exchanger (AE1). Semin Hematol 30:34, 1993

8. Jarolim P, Palek J, Amato D, Hassan K, Sapak P, Nurse GT, Rubin HL, Zhai S, Sahr KE, Liu SC: Deletion in erythrocyte band 3 gene in malaria-resistant Southeast Asian ovalocytosis. Proc Natl Acad Sci USA 88:11022, 1991

9. Mueller TJ, Morrison M: Detection of a variant of protein 3, the major transmembrane protein of the human erythrocyte. J Biol Chem 252:6573, 1977

10. Jarolim P, Rubin HL, Zhai S, Sahr KE, Liu SC, Mueller TJ, Palek J: Band 3 Memphis: A widespread polymorphism with abnormal electrophoretic mobility of erythrocyte band 3 protein caused substitution AAG → GAG (Lys → Glu) in codon 56. Blood 80:1592, 1992

11. Palatnik M, Simoes MLM, Alves ZMS, Laranjeira NS: The 60 and 63kDa proteolytic peptides of the red cell membrane band 3 protein: Their prevalence in human and non-human primates. Hum Genet 86:126, 1990

12. Ranney HM, Rosenberg GH, Morrison M: Frequencies of band 3 variants of human red cell membranes in some different populations. Br J Haematol 76:262, 1990

13. Gallagher PG, Forget BG: Spectrin genes in health and disease. Semin Hematol 30:4, 1993

14. Schofield AE, Reardon DM, Tanner MJ: Defective anion transport activity of the abnormal band 3 in hereditary ovalocytic red blood cells. Nature 355:836, 1992

15. Clark MR, Mohandas N, Shohet SB: Osmotic gradient ektacytometry: Comprehensive characterization of red cell volume and surface maintenance. Blood 61:899, 1993