SICKLE-CELL HAEMOGLOBIN K DISEASE

BY

P. O'GORMAN, M.D.

Consultant Pathologist, Brook General Hospital, London

KATHLEEN M. ALLSOPP, M.B., B.S.

Paediatric House-physician, Brook General Hospital, London

H. LEHMANN,* M.D., Sc.D., M.R.C.P., F.R.I.C.

Reader in Chemical Pathology and Honorary Director M.R.C. Abnormal Haemoglobin Research Unit, St. Bartholomew's Hospital, London

P. K. SUKUMARAN

Research Assistant, St. Bartholomew's Hospital, London

Haemoglobin K is a "fast" haemoglobin—that is, on electrophoresis at pH 8.6 it moves towards the anode in front of normal adult haemoglobin (Hb A). Hb K was first discovered in Berbers in Algeria by Cabannes and Buhr (1955). A haemoglobin with identical electrophoretic mobility was described from Liberia as "Liberian II" (Robinson, Zuelzer, Neel, Livingstone, and Miller, 1956). Further examples of Hb K were found in West Africa in Dagomba by Edington and Lehmann (quoted by Ager and Lehmann, 1958) and in an East Indian family (Ager and Lehmann, 1957). Other reports came from St. Thomas Island (Trincão, Franco, Gomes, and Ferreira, 1958) and Guinea (Trincão, Franco, and Nogueira, 1960). We have now found this haemoglobin in a West Indian family of West African stock, where in two members it was associated with sickle-cell haemoglobin (Hb S).

Hb S has been observed before with other variants of adult haemoglobin—for example, with Hb C (Itano and Neel, 1950), Hb D (Itano, 1951), Hb E (Aksoy and Lehmann, 1957), Hb G (Schwartz and Spaet, 1955), Hb J (Went and MacIver, 1959), and Hb O (Ramot, Fisher, Remez, Schneerson, Kahane, Ager, and Lehmann, 1960). Hb S always formed the major part and there was some sickle-cell disease—although it was milder than the homozygous sickle-cell anaemia. In these combinations Hb S is found with another β -chain abnormal haemoglobin, and no Hb A could therefore be synthesized. In the case of Hb S-O disease, some Hb A was found; but this observation could not be repeated later on, and it must be assumed that in spite of the denial by the parents of the patient there had been a previous blood transfusion (Baglioni and Lehmann, 1962).

Hb S has also been found in association with Hb Hopkins II (Smith and Torbert, 1958) and Hb P (Dherte, Lehmann, and Vandepitte, 1959). Hb Hopkins II is an α -chain abnormal haemoglobin, and some evidence for this has also been obtained in the case of Hb P, although in this case it is not satisfactory. In these two conditions Hb A was also present, the proportion of Hb S was less than half of the total pigment, and there was not even a mild sickling disease.

Sickle-Cell Haemoglobin K Disease

We recently examined the parents of a child with sickle-cell trait (A+S) and a number of other unrelated conditions. The mother also had the sickle-cell trait, but the father possessed Hb S and one other "fast" haemoglobin which was not Hb A (Fig. 1). He was not anaemic but had a history of occasional joint pains. The spleen was not palpable. The haematological findings in this subject were (see Fig. 2): Hb 15.1 g./100 ml.; R.B.C. 6,100,000/c.mm.; P.C.V. 52%; reticulocytes 1.2%; total W.B.C. 4,000/c.mm. No abnormality in serum proteins, urine. Serum iron 132 μ g./100 ml.

The fast haemoglobin, amounting to 40%, moved on paper and on starch electrophoresis at pH 8.6 and 8.9 in front of Hb A but behind Hb J. When Hb A was added

it could not be separated from the fast haemoglobin on paper electrophoresis at pH 6.8 or on IRC 50 resin chromatography at pH 6. The fact that only Hb S and Hb K were found indicated that this Hb K was a β -chain abnormal variant. This was confirmed by "hybridization" of the isolated Hb K fraction with the α -chain abnormal Hb Beilinson. This haemoglobin (De Vries, Joshua, Lehmann, Hill, and Fellows, 1963) moves behind Hb A at electrophoresis at pH 8.5—the pH of the starch-gel TRIS-borate discontinuous buffer system. When a mixture

FIG. 1.—Filter-paper electrophoresis pH 8.9. Left: father, Hb S+K. Middle and right: child and mother, sickle-cell trait (Hb A+S). TRIS buffer (Cradock-Watson, Fenton, and Lehmann, 1959).

FIG. 2.—Blood smear from case with sickle-cell/haemoglobin K disease ($\times 750$; stained with eosin).

of the two haemoglobins Beilinson and K was dissociated and re-combined, a third fraction appeared on starch-gel electrophoresis in the position of Hb A, presumably consisting of both Hb A and the doubly abnormal hybrid. The latter would move in the region of Hb A because the slower movement of the α -chains of Hb Beilinson would balance the faster movement of the β -chains of Hb K (Fig. 3).

We obtained by the kind offices of Dr. V. I. Massiah, Port of Spain, Trinidad, the blood of two maternal aunts of

*Now University Biochemist, Addenbrooke's Hospital, Cambridge.

the man with Hb S and Hb K, and one of them showed the same picture—that is, Hb S and Hb K were found but Hb A was absent. All were natives of the British West Indies and of no other known origin except West African.

FIG. 3.—Hybridization of haemoglobins Beilinson and the present K (for details of technique see Raper, Gammack, Huehns, and Shooter, 1960). Hb Beilinson is an α -chain abnormal variant, and, after dissociation with Hb K and recombination, electrophoresis on starch gel clearly shows an additional fraction due to the formation of Hb A and Hb Beilinson/K; these two haemoglobins migrate as one fraction (see text). Left—before; right—after dissociation and recombination.

Discussion

The definition of Hb K is that it is a Mendelian co-dominant variant of adult haemoglobin which can be separated by electrophoresis from Hb A, where at pH 8.6 it moves just slightly ahead of Hb A and behind Hb J.

Electrophoretic and chromatographic properties are the outcome of molecular shape and the charges of the molecule. It is clear that the same electrophoretic properties can come about for different reasons. Thus amino-acid substitutions may occur in the α - or β -chain and yet the electrophoretic behaviour of the resulting haemoglobins may be the same. The Hb K found in East

Indians is an α -chain abnormal haemoglobin (K_α) whereas the haemoglobin at present under investigation is clearly a K_β .

The result of double heterozygosity for Hb S and Hb K falls well into the not unusual pattern of only mild sickle-cell disease arising from the combination of Hb S with another β -variant of Hb A. However, it is known in the case of sickle-cell/Hb C disease and sickle-cell/Hb E disease that the people affected, though apparently quite healthy, are liable to develop anaemia with clinical manifestations when exposed to stress of any kind.

Summary

In a West Indian and his maternal aunt, sickle-cell haemoglobin was found in the hitherto undescribed association with haemoglobin K. No haemoglobin A was present. Recombination experiments demonstrated that this haemoglobin K was a β -chain abnormal variant. There was no anaemia, and a history of occasional joint pains was the only complaint which might be related to "sickle-cell haemoglobin K disease."

We should like to thank Dr. G. Slot, under whose care the child who was investigated originally was admitted, for giving us the facilities to study its parents, and Dr. W. E. Miall and Dr. V. I. Massiah for helping us to trace relatives in the West Indies.

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SERUM-VITAMIN-A LEVELS IN TWO FAMILIES WITH TYLOSIS*

BY

LESTER WEISS, B.S., M.D.

VICTOR H. AUERBACH, A.B., A.M., Ph.D.

ANGELO M. DiGEORGE, B.A., M.D., M.A.(Ped.)

From the Departments of Pediatrics and Physiological Chemistry, Temple University School of Medicine and St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

Tylosis palmaris et plantaris, a disease inherited as an autosomal dominant, is characterized by varying degrees of hyperkeratosis of the skin of the palms of the hands and soles of the feet. Anderson and Klintworth (1961) reported on a family with tylosis and clinodactyly. They found an associated hypovitaminosis-A in eight members of the family. The authors speculated upon the relationship between vitamin-A levels and tylosis palmaris et plantaris.

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although they recognized that their findings might have been purely coincidental.

We wish to present our findings of a study of two families in which tylosis was present and in which vitamin-A levels were determined in a total of 23 affected individuals. In all instances vitamin-A levels were found to be within normal range.

Material and Methods

The propositus of Family I (D.D., St. C.H.C. No. 612654), a 21-months-old white boy, came to our attention when he was admitted for evaluation of an episode of