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Effect of Maternal Sickle-cell Trait on Perinatal Mortality

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Summary

Possession of the sickle-cell trait (Hb AS) by the African mother has been shown to be associated with a significant increase in perinatal mortality when there is anoxic stress. This observation should be taken into consideration in the management of labour of both the indigenous and immigrant mothers at risk. The findings do not influence the proposed explanations for the maintenance of high frequencies of the haemoglobin S gene in areas of endemic malaria.

Introduction

The in-vitro and in-vivo formation of sickle-cells depends on a lowering of the oxygen tension (Hahn and Gillespie, 1927; Harris *et al.*, 1956), but the erythrocytes of the sickle-cell trait (Hb AS) do not sickle under usual venous oxygen tensions, a level as low as 15 mm Hg being required (Allison, 1956). Sickle-cell trait is associated only with serious life-threatening complications in the presence of unusual degrees of arterial oxygen desaturation. Clinical evidence of intravascular sickling in individuals with Hb AS was first noted in the second world war in Negro Service men flying in unpressurized aircraft (Smith and Conley, 1955), and the occurrence of sickling in other clinical situations has been reviewed (Levin, 1958; Necheles *et al.*, 1969).

The incidence of the sickle-cell trait is variable in its distribution among Negroes, the highest rates occurring in areas of holoendemic malaria (Huehns and Shooter, 1965; Jonxis, 1965). Several mechanisms have been proposed to account for the maintenance of the high frequencies of the haemoglobin S genes in malarious regions (Allison, 1954; Raper, 1955, 1959; Garlick, 1960; Motulsky, *et al.*, 1966), including the proposition that there is increased fertility among females possessing the sickle-cell trait (Edington, 1955; Livingstone, 1957; Delbrouck, 1958; Firschein, 1961).

In the present study the possibility of a selection factor operating against the sickle-cell trait was investigated.

Material and Methods

A perinatal mortality survey was conducted at University College Hospital, Ibadan, Nigeria, the survey period extending

from 1961 to 1964 covering 27 selected months (Platt, 1970). Necropsies were performed by one investigator on all perinatal deaths of infants over 500 g in weight occurring among booked and emergency admissions. A pathological classification for the cause of death was used based on that originally described by Bound *et al.* (1956), and subsequently adopted for the British National Perinatal Mortality Survey (Butler and Bonham, 1963).

An assessment of the clinicopathological associations was made in all cases of perinatal death, and details were obtained concurrently on all the "normal" deliveries occurring within the survey period.

Mothers were booked for delivery either because they had a previously poor obstetric history or because complications were deemed probable, the chief indication being potential mechanical difficulties in labour. A sickling test with 2% sodium metabisulphite was performed on all mothers making their first visit to the various antenatal screening clinics that were held at other hospitals. In the event of a positive sickling test further electrophoretic studies were performed and those possessing either Hb SC or more rarely Hb SS were booked for delivery. In addition to normal obstetric care mothers received anti-malarial drugs and folic acid during pregnancy.

The emergency admissions were either referred from other hospitals and domiciliary centres or came direct from homes in the town or outlying villages. Mothers would be admitted having a wide range of one or more obstetric or medical complications, though mechanical difficulties in labour, severe megaloblastic anaemia, and antepartum haemorrhage predominated. After admission the haemoglobin genotype was determined, care being taken to differentiate between the mother's true genotype and transfused blood that might have come from a Hb AS donor.

Results

In the survey period there were 435 singleton perinatal deaths and 4,148 singleton deliveries. Table I shows the rate per thousand (booked and emergency) deliveries of babies dying when the necropsy findings were predominantly those of anoxia. One in 20 of the booked and one in four of the emergency deliveries resulted in a perinatal death. Over half of all the singleton deaths were associated with anoxic stress occurring in the antepartum or intrapartum period; in the latter group birth trauma was apparent in some instances, and the risk ratio for an intrapartum death was one in 43 of all booked and one in seven of all emergency deliveries.

There was no selection of mothers with the sickle-cell trait for hospital delivery at U.C.H., Ibadan (Table II). The incidence of Hb AS among Yoruba blood donors and the booked mothers was identical and the same trend existed for emergency deliveries.

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TABLE I—Perinatal Mortality Rates for Booked and Emergency Deliveries

Major Necropsy Finding	Perinatal Mortality Rate per 1,000 Deliveries	
	Booked	Emergency
Antepartum death with anoxia	4.1	28.7
Intrapartum death with anoxia ± birth trauma	15.6	113.6
All perinatal deaths	54.0	251.0

TABLE II—Frequency of Various Haemoglobin Genotypes among Yoruba Blood Donors and Mothers Booked for Delivery at U.C.H., Ibadan

Source of Material	Haemoglobin Genotype				No. of Individuals
	AA	AS	AC	Others	
Blood Donors 1957-9 (Watson-Williams, 1965)	70.8%	23.6%	4.8%	0.8%	12,387
Booked mothers survey period	71.2%	23.9%	4.5%	0.4%	2,956

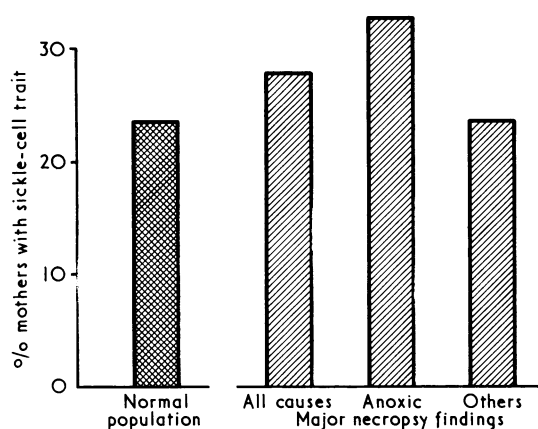
The distribution of the maternal genotype for all anoxic deaths and for deaths associated with "other" pathological findings among 408 perinatal deaths is shown in Table III. Excluded from the series were 15 mothers in whom an accurate record of their haemoglobin genotype could not be obtained and 12 mothers who were either Hb SC or Hb SS. The booked and emergency deliveries were combined because the occurrence of Hb AS trait was identical in both categories.

TABLE III—Frequency of Maternal Haemoglobin Genotype for Perinatal Deaths due to Anoxic and "Other" Pathological Findings

Major Necropsy Finding	Maternal Haemoglobin Genotype		
	AA	AS	AC
All anoxic deaths	145 (63.9%)	74 (31.6%)	8 (3.5%)
Other pathological findings	126 (69.6%)	43 (23.8%)	12 (6.6%)
Total	271 (66.4%)	117 (28.7%)	20 (4.9%)

The distribution of the Hb AS genotype among the various subgroups with "other" pathological findings contained two frequencies of importance. For those perinatal deaths which occurred in the antepartum period and where no major pathological lesion was observed the proportion of mothers with Hb AS was low as 18% and that for babies dying of "respiratory distress syndrome" (hyaline membrane) the figure was as high as 32%.

The findings for the maternal sickle-cell trait alone are shown in the Chart. There was a significant difference between



Frequency of the sickle-cell trait among mothers who had a perinatal death grouped as "all causes" of death and as "anoxic" or "other" major necropsy findings.

the frequency of mothers in the normal population with Hb AS (23.6%) and those mothers with the trait for whom a perinatal death occurred, all causes combined (28.7%) (χ^2 , $n = 1$, $P < 0.05$).

When the distribution of maternal Hb AS was analysed for the two major groups, anoxic perinatal deaths and "other" pathological findings, the latter group was identical to that of the normal obstetric population, 23.8%. The difference in the incidence of Hb AS among the mothers whose infants died of anoxic stress (32.6%) compared with those mothers whose infants died of other causes was significant (χ^2 $n = 1$, $P < 0.05$) and an even greater difference existed between the maternal Hb AS anoxic death group and the normal obstetric population (χ^2 , $n = 1$, $P < 0.01$).

Discussion

Agonal sickling of red cells has always been readily observed in the necropsy and biopsy material of individuals possessing some degree of S haemoglobin, and this was a consistent feature in all placentae examined from mothers with the sickle-cell trait or who had received some transfused blood from a Hb AS donor. The present observations which indicate an association between mothers with sickle-cell trait and a higher perinatal mortality when there was concomitant anoxic stress may be explained on the basis of in-vivo sickling. It is probable that oxygen tensions less than 15 mm Hg are attained in the placental bed when factors that produce antepartum and intrapartum anoxia are present; the in-vivo sickling of maternal red cells in the placental sinusoids may worsen an already critical situation for the fetus, resulting in intrauterine death.

Further evidence for the above proposition comes from the studies of Johnson and Ojo (1967) on amniotic fluid oxygen tension in anaemic and non-anaemic African mothers. Four of the five perinatal deaths reported in their series occurred among the anaemic mothers where the amniotic fluid tension was in the range of 8 to 18 mm Hg, the maternal haemoglobin genotype in all four cases was Hb AS.

The high frequency of sickle-cell trait among mothers whose infants died of "respiratory distress syndrome" (hyaline membrane) may have been the result of a greater degree of anoxic stress occurring during labour as a consequence of in-vivo sickling. Anoxia is an important associated factor in the aetiology of "respiratory distress syndrome" (Reynolds, 1970), and in the Ibadan series the syndrome resulting in a perinatal death occurred four times more frequently in second twins than in the first twin, confirming the observations of other workers (Crosse, 1957; Keuth *et al.*, 1964; Rokos *et al.*, 1968).

There is a paucity of literature on the subject of perinatal mortality among Africans, but all the published evidence (Lawson and Lister, 1954; Dodge and McKinney, 1964; Brown and Sandhu, 1966; Grech, 1967; Lawson and Stewart, 1967) and the experience of obstetricians indicate that mechanical difficulties in labour resulting in intrapartum death with anoxia is the major obstetric problem in tropical Africa. Since hospital services are limited in developing countries there is inevitably a high degree of selection of those cases most likely to present difficulties in labour. At U.C.H., Ibadan, the booked lower segment caesarean section rate was 200 per 1,000 deliveries.

In practical terms it is suggested that the maternal genotype should be determined as a routine and that mothers possessing the trait may, in the event of complications occurring in labour that result in fetal distress, require more active management than has been practised hitherto.

Though the possession of sickle-cell trait may influence the management of labour on an individual basis, the overall effect of the increased perinatal loss on the balanced polymorphism of the haemoglobin S gene is uncertain in areas of endemic malaria. Differential mortality operating primarily on children was the initial concept for explaining the maintenance of the

haemoglobin S gene in the population (Allison, 1954; Raper, 1955, 1959; Garlick, 1960; Motulsky *et al.*, 1966), though there were extensive discrepancies between the number of Hb AA children who should die and the number that actually died. Subsequently evidence that there was an increased fertility among Hb AS females was proposed (Edington, 1955; Livingstone, 1957; Delbrouck, 1958; Firschein, 1961). More recently it had been suggested that a third mechanism may be operative in that there is enhanced fertility of the Hb AS male (Eaton and Mucha, 1971).

The data of Edington (1955) from Ghana and of Firschein (1961) from British Honduras showed that mothers with the sickle-cell trait had a fertility ratio which could account for the value required to maintain the local sickle-cell trait frequency. Edington also showed that the stillbirth rate for a hospital population of mothers with Hb AS was slightly lower, but the figures were not at acceptable levels of statistical significance. In the current study the finding of a low frequency of Hb AS mothers who had an antepartum death of their fetus showing no significant pathological lesion supports the observations of other workers that the incidence of abortion and antepartum stillbirths is lower among such mothers (Garnham, 1949; Bruce-Chwatt, 1952).

With the generally accepted evidence that there is a higher fertility rate among mothers with the sickle-cell trait, and in the absence of data other than that from "selected" hospital populations, it is justified, at present, to assume that greater perinatal loss associated with the maternal sickle-cell trait is an observation of relevance to the practical management of the labour of an individual possessing the trait but that the overall perinatal loss does not influence the balanced polymorphism of the haemoglobin S gene.

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PRELIMINARY COMMUNICATIONS

Multiple Drug Therapy for Disseminated Malignant Tumours

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Summary

Forty patients with various disseminated malignant tumours were treated with up to six antitumour drugs given for periods not exceeding 24 hours. Complete or partial objective tumour regression was achieved in 20 patients. No regression occurred in the remaining 20. Treatment given in this way

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seemed to be at least as effective as other multiple drug regimens and had the following advantages: (1) toxicity was reduced to a minimum and no access was needed to sterile rooms or platelet transfusions since severe bone marrow depression did not occur, and (2) the patients spent only a very short time in hospital.

Introduction

In recent years it has become apparent that antitumour drugs are often more effective when given in combination than when given singly or in sequence. This has been observed particularly in acute leukaemias and malignant lymphoma. Thus the treatment of these diseases with single agents produces complete remission in from 25 to 50% of patients, whereas with judicious combinations of three or four drugs the proportion of complete remissions has been increased to 85% in acute lymphoblastic leukaemia and Hodgkin's disease. These observations have naturally led clinicians to apply combination schedules to patients with disseminated solid tumours which could not be treated by local methods such as surgery or radiotherapy. Thus, for example, Costanzi and Coltman (1969)