Iron deficiency in sickle cell anaemia

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SUMMARY Thirty-seven patients with SCD were studied: 24 were diagnosed as homozygous Hb S on the basis of their haematological findings, and α:non-α globin chain ratios were found to be balanced in all. Thirteen patients were thought to have α or β thalassaemia interaction with Hb S on the basis of low MCV and MCH, family history and/or presence of Hb A on electrophoresis. Six of them had abnormal α:non-α ratio (one had a ratio of 0·72 suggestive of α thalassaemia, and five had ratios between 1·4 and 1·9, compatible with β thalassaemia interaction). The remaining seven patients with microcytosis had balanced globin chain synthesis and five were found to be iron deficient. Five additional patients (3 with Hb SS and 2 with Hb S/β thalasseamia) had lower than normal serum ferritin concentration. The analysis of case histories disclosed that peptic ulceration, recurrent epistaxis and multiple pregnancies could account for iron loss in seven patients. These findings indicate that iron deficiency may be common in SCD and should be excluded as a cause of microcytosis.

Microcytosis, in the absence of conclusive family studies and/or presence of Hb A on electrophoresis, is an unreliable indicator of α or β thalassaemia interaction with Hb S.

It is always assumed that individuals with inherited severe haemolytic anaemia have iron overload due to increased iron absorption[1] from the gut and to repeated transfusions of blood. Iron deficiency is considered unlikely, and in sickle cell disease (SCD) microcytosis, defined by low MCV and MCH is taken to indicate the presence of an interaction with α or β thalassaemia. Recent studies[2-4] have confirmed this view by showing that individuals homozygous or heterozygous for α thalassaemia and Hb S have significantly lower MCV and MCH than those with a normal α gene complement. The presence of microcytosis in patients with Hb S/α or β thalassaemia is well documented.[5]

The published data on iron status in SCD tends to confirm that excess iron is present: high serum ferritin concentration is commonly found,[6-8] even in patients whose bone marrow iron stores are absent.[7] There are, however, reports to the contrary: O'Brien[8] reported that patients with SCD do not acquire excessive iron burden during the first two decades of life, and iron deficiency in young children with sickle cell disease has been described.[8 10] Vichinsky and colleagues[10] treated six iron deficient

children with iron; there was an increase in Hb and a normalisation of red cell indices in all.

We have studied 37 adults with SCD, 13 of whom had low MCV and MCH and were thought to have either α or β thalassaemia interaction with Hb S. We wish to report the results of studying their iron status and their globin chain synthesis.

Patients and methods

PATIENTS

Thirty-seven patients with SCD in the steady state and at least six months after the last blood transfusion were studied. No patient had any renal function impairment. There were 18 women (mean age 21·3, range 12–45 yr) and 19 men (mean age 22·8, range 13–35 yr). Thirteen patients were thought to have Hb S/α or β thalassaemia interaction on the basis of low MCV and MCH, presence of small amounts of Hb A (9–12%) on electrophoresis, or family studies, or a combination of these. The details of the thirteen patients are shown in the Table. The remaining 24 patients were diagnosed as Hb SS, and their haematological variables are shown at the bottom of the Table.

METHODS

Values for Hb, MCV and MCH were obtained using a Coulter Model S. Hb A2 was measured using

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Details of patients studied

Case	Sex/Age (yr)	Hb (g/dl)	MCH (g/l)	A2 %	F %
1	F/19	9·3	22·4	2·2	10·6
2*	M/20	10·7	23·6	2·0	2·1
3*	F/45	11·2	23·1	4·8	5·7
4†	M/21	8·6	23·8	5·2	0·9
5†	F/26	9·1	25·0	1·9	1·3
6	M/21	8·8	20·8	3·4	6·0
7	M/22	8·1	25·3	2·7	1·2
8	M/25	9·2	24·2	2·7	1·4
9	M/14	6·5	26·4	1·6	1·5
10	M/25	10·1	26·9	3·1	4·0
11	M/18	13·3	26·6	2·5	3·4
12	F/24	12·8	24·5	2·5	2·0
13	M/19	12·8	22·0	5·7	4·8
14–37	14F, 10M	8·47	29·0	2·28	6·7
		7·1–9·9	24·2–34	1·0–3·1	0·9–16·8

*Mother and son.
†Brother and sister.
Cases 1–13 were though to have Hb S/thalassaemia interaction; cases 14–37 to have homozygous sickle cell anaemia.

Helena Laboratories scanning equipment of cellulose acetate strip. Hb F was measured by the method of Betke *et al.*[11] Serum iron and total iron binding capacity (TIBC) were measured according to Young and Hicks.[12] Serum ferritin concentration was measured with the Becton Dickinson radioimmune assay kit, using the method of Addison *et al.*[13] The manufacturers suggest a normal range for women of 25–250 μg/l, and of 50–500 μg/l for men. Globin chain synthesis was estimated by the method of Clegg *et al*;[14] the results were expressed as α:non-α ratio. The normal range of α: non-α ratios on nine healthy laboratory controls was 0·88–1·16. The error of the method, calculated from 14 duplicate measurements was ±0·03.

Results

The α:non-α globin chain synthesis ratios for the 37 patients are shown in Fig. 1. Cases 14–37, previously diagnosed as Hb SS, all had α:non-α ratios between 0·84 and 1·27. Of the 13 patients thought to have thalassaemia/Hb S interaction, six had abnormal α:non-α ratios (case 1 ratio of 0·72, and cases 3, 10, 11, 12 and 13 ratios of 1·4 and over), whereas the remaining seven patients (cases 2, 4, 5, 6, 7, 8, 9) had α:non-α ratios ranging from 0·84–1·17.

Serum iron, TIBC and ferritin concentration are shown in Figs. 2 and 3. It is clear from these data that patients with microcytosis and balanced globin
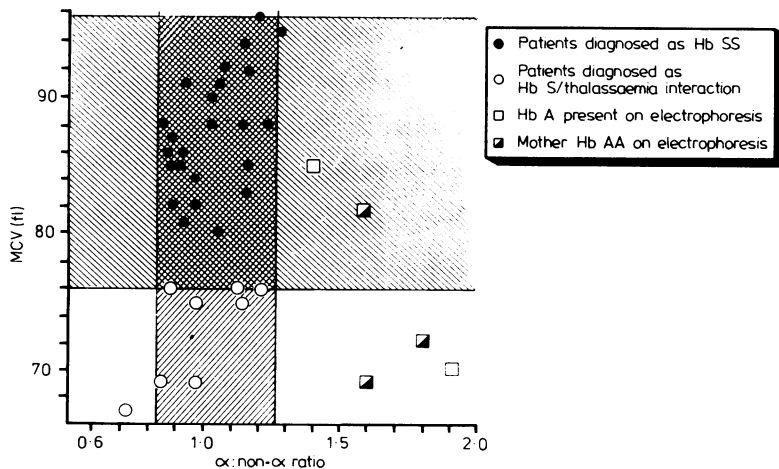

Fig. 1 *The plot of MCV against α:non-α ratio in SCD. Shaded area denotes the normal range.*

Serum iron

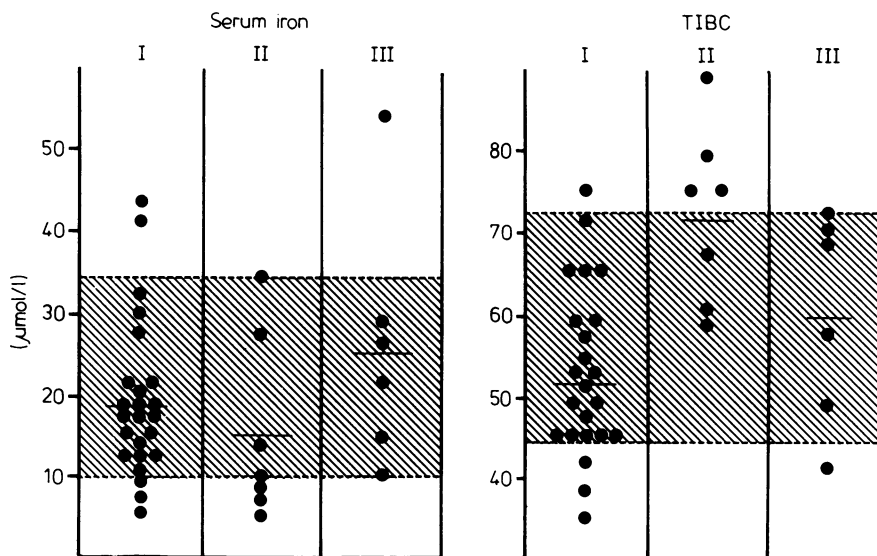I   II   III

TIBC

I   II   III

Fig. 2   *Serum iron and total iron binding capacity in SCD. Group I: patients with normal MCV and balanced α:non-α ratio. Group II: patients with microcytosis and normal α:non-α ratio. Group III: patients with abnormal α:non-α ratio. Horizontal lines denote normal range and mean.*
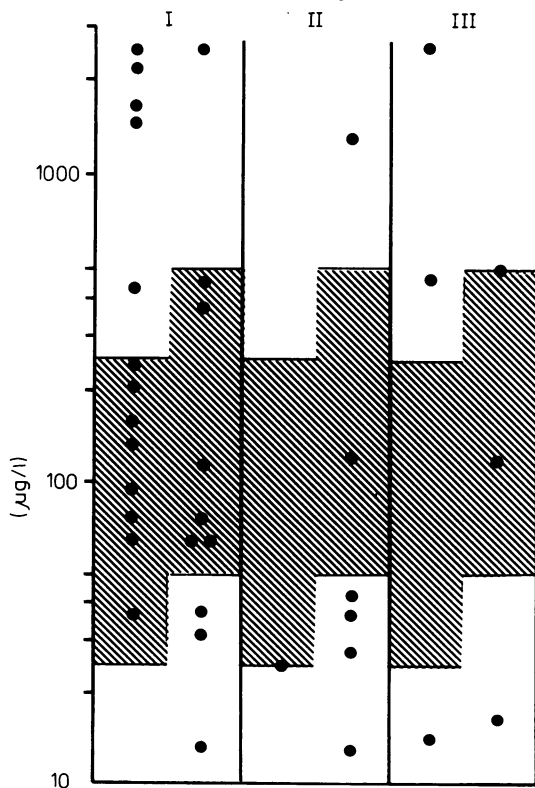
I   II   III

Fig. 3   *Serum ferritin in SCD. Groups as for Fig. 2. Females on the left, males on the right of each column. Horizontal lines denote normal range.*

chain synthesis had significantly higher TIBC and lower ferritin concentration than those with normal red cell indices (p < 0·001 for TIBC; p < 0·05 for log ferritin using Student's t test).

Possible sources of iron loss were investigated for all patients. Five men had proven peptic ulcers, one had recurrent epistaxis and two women had multiple pregnancies without blood transfusion or iron supplementation. Of these eight patients, seven had lower than normal serum ferritin concentration, high TIBC and microcytosis; globin chain synthesis was balanced in five. Two patients in this group, both with balanced globin chain synthesis, required surgical treatment for peptic ulcer. Liver biopsy was carried out at operation, and stainable iron was absent in both biopsies. Three additional patients were iron deficient, but no source of iron loss could be found.

Discussion

In the absence of conclusive family history or Hb A on electrophoresis, microcytosis is unreliable as an indicator of α or β thalassaemia interaction with Hb S. In our series, seven patients with low MCV and MCH had balanced globin chain synthesis, and five were found to have lower than normal serum ferritin concentration and higher TIBC.

There is no evidence of increased iron load in sickle cell disease, and iron deficiency may be more common than suspected, especially in men. The aetiology of iron loss is not clear, but GI tract bleed-

ing due to peptic ulceration, epistaxis and multiple pregnancies can account for iron lack in seven of our patients. Iron loss in urine may also be responsible. Even in the steady state, SCD patients excrete variable but generally larger than normal amounts of iron.[15] During crises, when marked intravascular sickling and haemolysis occur, the amount of iron lost in urine may be much greater.

The effect of iron deficiency on α:non-α ratio in sickle cell anaemia and sickle thalassaemia is not known. Walford and Deacon[16] have shown that iron deficiency reduces the α/β chain imbalance in β thalassaemia trait. It is thus possible that on correction of iron deficiency some of our patients may alter their α:non-α ratio and an imbalance in globin chain synthesis becomes apparent. Should this be true, one can hypothesise that individuals with α and β thalassaemia/Hb S interaction have a propensity to develop iron deficiency, perhaps because their Hb, PCV and RBC count are higher than in those with Hb SS.[45] The higher count and the subsequent higher blood viscosity may be responsible for the high incidence of peptic ulceration or increased urinary iron loss. Further studies are required to elucidate these points.

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