SICKLE-CELL ANAEMIA COMPLICATED BY MEGALOBlastic ANAEMIA OF INFANCY

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The association between megaloblastic anaemia and various haemolytic anaemias is well documented. The most recent publications on the subject are by Chanarin *et al.* (1959) and Jönsson *et al.* (1959). The latter authors review 13 cases from the literature, and add three cases of their own. Two of these had sickle-cell anaemia, and the third sickle-cell/haemoglobin-C disease. These three cases are the first examples of such a combination in adults we could find in the literature.

The purpose of this communication is to report five cases of megaloblastic anaemia associated with sickle-cell anaemia. These five cases were found in a series of 50 cases of megaloblastic anaemia of infancy attributable to folic-acid deficiency (MacIver and Back, 1960). We have been able to find only one other report in the literature of this association in infancy (Zuelzer and Rutzky, 1953).

Methods

Standard haematological methods were used (Whitby and Britton, 1957). *In vitro* sickling tests were carried out, using 2% sodium metabisulphite (Daland and Castle, 1948). Filter-paper electrophoresis of haemoglobin was performed in a horizontal tank using barbitone buffer of pH 8.6 and ionic strength about 0.02 (Went and MacIver, 1956). Foetal haemoglobin was determined by the alkali denaturation technique described by Singer *et al.* (1951).

Bone-marrow aspiration was carried out using an Osgood (16 gauge) needle under local anaesthesia. The site of puncture selected was the upper end of the tibia about 2 in. (5 cm.) below the tibial tuberosity. The marrow films were stained by both Leishman's method and the May-Grünwald-Giemsa technique. A portion of the aspirated material was allowed to clot in the syringe, and the specimen so obtained was fixed and sectioned histologically as described by Mertens (1945). The sections were stained with haematoxylin and eosin, and for iron by the Prussian-blue technique of Perls.

Pertinent Haematological Data

Case No.	Sex	Age (Months)	On Admission				Days After Beginning of Folic-acid Therapy	On Discharge		
			Hb (g./100 ml.)	Reticulocytes (%)	W.B.C.	Nucleated Red Cells/100 W.B.C.		Hb (g./100 ml.)	Reticulocytes (%)	Foetal Hb (%)
1	M	12	2.8	1	24,000	63	15	6.6	30	0-54
2	M	14	3.2	12	12,000	164	3	6.5	10	14
3	M	12	3.6	5	22,000	57	4	6.0	28	10
4	F	10	4.1	11	4,000	469	7	8.0	32	16
5	F	13	3.2	5	18,000	6	6	9.0	30	94
Mean		12	3.4	7	16,000		7	7.2	26	11

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All the sections were stained for iron simultaneously to minimize technical errors.

The relevant haematological findings are given in the Table.

Case 1

A male infant, aged 1 year on his first admission to hospital, had developed fever and yellow eyes at the age of 6 months, and the jaundice had been present ever since. He suffered from attacks of fever every two or so weeks. He was breast-fed for eight months, and then weaned on to "quaker" oats and condensed milk, with "ovaltine" at night and one egg a week.

On examination he was very anaemic and slightly jaundiced. His nutritional state was poor — weight 13 lb. 14 oz. (6.3 kg.). The hair was sparse, wiry, and reddish in colour. The liver and spleen could not be felt, but a few small, shotty, mobile glands were palpable in all areas. There was minimal oedema of the feet. The *in vitro* sickling test was positive. A diagnosis of sickle-cell anaemia was made. As his general condition was fair he was observed for a few days and treated with intramuscular iron. After blood transfusions he was discharged with a haemoglobin level of 12.4 g./100 ml.

Fifty-five days later he was readmitted with a story that he had remained well until three weeks previously, when he developed a chest cold and fever. A week before admission he began vomiting after his feeds, but he had no diarrhoea.

On examination the child was miserable and cried constantly. His nutritional state was poor (weight 11 lb. 8 oz.—5.2 kg.), and he was obviously anaemic. The hair was dry, reddish in colour, and sparse. There was no oedema. The haemoglobin level was 6.3 g./100 ml., the white-cell count 2,600/c.mm., the reticulocyte count 0.4%, and, surprisingly, in view of the previous diagnosis of sickle-cell anaemia, haemoglobin electrophoresis revealed

FIG. 1A

FIG. 1B

FIG. 1.—Case 1. Sickling preparations of the blood (A) on second admission, (B) six days after the beginning of folic-acid therapy.

haemoglobin type A only, and the *in vitro* sickle-cell test was negative. A closer examination of the sickle preparation showed, however, that about 1% of the red cells were in fact sickling (Fig. 1 A). As there was no reason to doubt the original diagnosis of sickle-cell anaemia (though haemoglobin electrophoresis had not been performed during

FIG. 2.—Case 1. Bone-marrow before the beginning of folic-acid therapy on second admission, showing changes in the granulocytes characteristic of megaloblastic anaemia.

the previous admission) it was thought that folic-acid deficiency was likely and that his red cells consisted largely of those transfused on the earlier admission. The bone-marrow was therefore examined, and found to be megaloblastic (Fig. 2). Treatment with folic acid (10 mg. per day) was instituted and a striking reticulocytosis resulted which reached a maximum of 50% 15 days after beginning treatment (Fig. 3). A repeat sickling test after six days of folic acid showed that about 20% of the cells sickled

preceding month. He had been breast-fed for eight months and then weaned on to "ostermilk" and "milo" sweetened with condensed milk. He also received soup, fish tea, Irish potatoes, bread, biscuit, and egg-white every other day. He was well until a month before admission, when he began refusing his feeds, and then lost weight. His mother noticed that his skin was becoming increasingly pale, and he developed a cold and cough with fever especially at night. His condition had deteriorated rapidly during the preceding week. At no time had he had diarrhoea or vomiting, and there was no history of jaundice.

On examination he was an extremely pale child of fair nutritional state—weight 17 lb. 7 oz. (7.9 kg.). The temperature was 101° F. (38.3° C.). There was no jaundice. Some frontal bossing of the skull was seen, and the hair was sparse. The skin was normal, and there was no oedema. A generalized slight lymphadenopathy was present, the liver was palpable 1½ in. (4 cm.) below the costal margin, and the spleen was also enlarged, being felt 1 in. (2.5 cm.) below the costal margin. The chest was clear.

Haemoglobin electrophoresis showed type S haemoglobin only. Bone-marrow biopsy revealed a frankly megaloblastic pattern (Fig. 4). A diagnosis of sickle-cell anaemia complicated by megaloblastic anaemia was made. A smear of peripheral blood was found to contain megaloblasts (Fig. 5).

Treatment with folic acid (10 mg. per day) was begun, and three days later the reticulocyte count had risen from an initial value of 12% to 30%. Ten days after the start of folic-acid therapy the haemoglobin level had risen to 6.7 g./100 ml., and when the child was seen on follow-up

FIG. 3.—Case 1. Curves from serial haemoglobin and reticulocyte estimations during the two admissions to hospital. The gap between days 19 and 74 days represents the period between the two admissions. The prolongation of the haemoglobin curve marked "Hb A" has been calculated from the percentage Hb S present in the total haemoglobin from quantitation of the paper electrophoretic strips on days 87 and 100.

(Fig. 1 B), and the reticulocyte count at this stage was 22%—from which it can incidentally be deduced that reticulocytes sickle. Examination of a further specimen after 19 days of folic-acid therapy showed that most of the red cells sickled. After 28 days of treatment the child was sent home with a haemoglobin of 6.6 g./100 ml.

Case 2

A male infant aged 14 months was admitted to hospital because of loss of appetite and progressive pallor during the

FIG. 4.—Case 2. Bone-marrow before the beginning of folic-acid therapy, showing megaloblastic erythropoiesis.

FIG. 5.—Case 2. Peripheral blood smear before the beginning of folic-acid therapy, showing megaloblasts.

a month later the haemoglobin level was 8.5 g./100 ml. and the reticulocyte count 13%.

Case 3

A male infant aged 1 year was admitted to hospital because of refusing feeds for three weeks and increasing pallor for one week. He had been breast-fed for six months, and was then weaned on to condensed milk and cornmeal porridge. Occasionally he was given cow's milk instead of condensed milk if any was available. He was apparently quite well until three weeks before admission, when he started to refuse feeds. Thereafter he deteriorated rapidly, losing weight and becoming increasingly pale. He had been feverish day and night for a week, but had no cold or cough. There was no history of vomiting or diarrhoea, and no history of jaundice.

On examination the child looked ill and extremely pale. The temperature was 101° F. (38.3° C.). His nutritional state was good—weight 19 lb. 4 oz. (8.7 kg.)—he was not dehydrated, and jaundice was absent. The lymphatic nodes were slightly enlarged in all areas. There were no skin or hair changes, but a trace of ankle oedema was observed. The liver was palpable 1½ in. (4 cm.) and the spleen ½ in. (1.3 cm.) below the costal margin. Haemoglobin electrophoresis showed type S haemoglobin only. Bone-marrow biopsy disclosed a strikingly megaloblastic pattern. A diagnosis of sickle-cell anaemia complicated by megaloblastic anaemia was made.

Treatment consisted of skimmed milk and mixed feeding, which he took well from the outset, and oral folic acid (10 mg. per day). Four days after the start of folic-acid therapy the reticulocyte count had risen from 2.5% to 46.5%, and the haemoglobin rose slowly to a maximum of 6 g./100 ml. There appeared to be a second reticulocyte response from treatment with oral iron.

Case 4

This infant was 10 months old when first seen in the paediatric out-patient department. She had had fever, a cold, and slight diarrhoea for a few days. Two months later she was admitted to hospital because of recurrent infections of the upper respiratory tract, associated with fever, and malnutrition. She had been breast-fed for three months, and then weaned on to skimmed milk supplemented with carrot juice and potato.

On examination she was miserable and malnourished—weight 13 lb. 15 oz. (6.3 kg.). The temperature was 103° F. (39.4° C.). The hair was sparse and silky, but there was no oedema. The liver-edge was just palpable, and the spleen was enlarged two fingerbreadths. There was no jaundice. A blood transfusion of 300 ml. was given. Haemoglobin electrophoresis on a post-transfusion sample of blood showed an S + A pattern (approximately 70% haemoglobin S and 30% haemoglobin A). It was thought likely that this represented the pattern of sickle-cell anaemia plus a minor fraction of normal haemoglobin derived from the transfused blood.

A bone-marrow aspiration revealed intense erythroid hyperplasia with some megaloblastic changes, and consequently treatment with folic acid (10 mg. per day) was begun. The reticulocyte count rose from 9% to 32% seven days later, and the haemoglobin level rose from 6.2 to 8.2 g./100 ml. in the same period.

Case 5

A female infant aged 13 months was admitted to hospital because of swelling of the ankles for one week and vomiting and diarrhoea for four days. She had been breast-fed twice daily, supplemented with "lactogen," for eight months, and then weaned on to oat porridge and condensed milk with an occasional addition of some skimmed milk to the porridge. Three months before admission to hospital she was seen in the casualty department because of fever and vomiting. She was noted to be undernourished at that time and suffering from an upper respiratory infection. She was

put on skimmed milk, and when seen again on two occasions she seemed to be improving. However, she was noticed to be pale, and cod-liver oil and iron were given.

On examination she was malnourished—weight 11 lb. 6 oz. (5.2 kg.)—and moderately wasted. She was slightly dehydrated but afebrile. Her mucous membranes were very pale, and there was some bilateral oedema of the ankles. The skin on the legs was dry and cracked; the hair was sparse but not depigmented. There was no jaundice. The liver was palpable 1½ in. (4 cm.) below the costal margin, but the spleen was not felt. There was no lymphadenopathy. Type S haemoglobin only was found on electrophoresis. Bone-marrow aspiration showed that erythropoiesis was megaloblastic in type. A diagnosis of sickle-cell anaemia complicated by megaloblastic anaemia was made.

An immediate blood transfusion of 100 ml. was given, followed by intravenous fluids. The vomiting was controlled by gastric lavage, and oral feeds were begun with clear fluids followed by gradually increasing strengths of skimmed milk. Folic-acid therapy (10 mg. per day) was begun on the

FIG. 6.—Case 5. Curves from serial haemoglobin and reticulocyte estimations.

second day, and six days later the reticulocyte count had risen from an initial value of 5% to 58% (Fig. 6). The haemoglobin level rose to 8.4 g./100 ml., and remained at about that level during the rest of her stay in hospital. A second, very marked reticulocyte response was noted as a result of oral iron. There was no significant further increase in haemoglobin.

Discussion

The incidence of sickling in a typical population group in Jamaica is 11% (Went, 1957), and one would therefore expect 3 cases of sickle-cell anaemia per 1,000 births. The fact that in a series of 50 cases of megaloblastic anaemia of infancy five were also suffering from sickle-cell anaemia is therefore highly significant, and it is likely that in Jamaica infants with sickle-cell anaemia are unusually prone to develop megaloblastic anaemia. The constant regenerative effort associated with the haemolytic process may be assumed to create a very heavy demand for haemopoietic substances, so that if there is an inadequate intake of such substances, or a diminished absorption as may occur with diarrhoea, a megaloblastic anaemia may result. This situation is even more likely to occur when the demand for haemopoietic substances is increased, as in periods of rapid growth and in pregnancy.

In megaloblastic anaemia of infancy it seems likely that the deficiency is mainly one of folic acid. The dietary intake of folic acid in infants in Jamaica must

be very near the borderline of adequacy in the post-weaning period. Milk, which is normally the chief staple of an infant's diet during the first year of life, has a low folic-acid content, and the Jamaican infant receives little or no fresh milk and only small quantities of condensed milk. The heating processes involved in the canning and powdering of milk further reduce the already low content of folic acid (Luhby and Wheeler, 1949). Three of the cases (Nos. 1, 4, and 5) were suffering from frank malnutrition which was comparable in degree to what is seen in other infants with megaloblastic anaemia. The other two cases, however, were moderately well nourished as judged by weight, but had been refusing their feeds during the three to four weeks previous to admission.

The only supplementary foods given to four out of the five infants were some cereals. Case 2 received a comparatively good diet, but green vegetables and meat, which are the best sources of folic acid, were not given. Though dietary inadequacy is probably the main factor in the aetiology of the megaloblastic anaemia in these five cases, it is likely that infection also played a part. The importance of infection in precipitating the condition has been stressed, and an increase in the requirements of ascorbic acid in infection is thought to be responsible (May *et al.*, 1952). The infection may sometimes be quite trivial and may have subsided with or without treatment before the anaemia becomes evident. Attacks of vomiting and diarrhoea, together with feeding problems, and mild infections of the upper respiratory tract were present in various combinations in the five cases described in this paper.

The most striking feature with regard to these children from a clinical point of view was the severe anaemia (see Table, p. 775). The average haemoglobin level on admission was 3.4 g./100 ml., which contrasts strikingly with our findings in 114 cases of sickle-cell anaemia (Went and MacIver, 1956; MacIver and Went, 1958; Went and MacIver, 1958), in which the average haemoglobin level was found to be 7.2 g./100 ml. In the 0-2 year age-group (19 cases) the average haemoglobin level was about the same (7.5 g./100 ml.) when four very low values due to associated megaloblastic anaemia were excluded. In addition, in our five cases with associated megaloblastic anaemia the reticulocyte counts were definitely lower (average 7%) than is usual in sickle-cell anaemia in this age-group (average 20.5%). Treatment with folic acid produced a very striking increase in the reticulocyte counts in every case, with a maximum response in an average of seven days after the start of folic acid therapy (see Table). A rise of haemoglobin followed to an average of 7.2 g./100 ml. and a fall in reticulocytes to an average of 26%, both of which must be regarded as normal values in sickle-cell anaemia.

The bone-marrow morphology varied from a gross megaloblastic change in Cases 1 and 2 (Figs. 2 and 4) to a less markedly abnormal, but none the less characteristic, picture in the other three cases. Nucleated red cells were often numerous in the peripheral blood, and in Cases 2 and 3 many of these were clearly megaloblasts.

Case 1 (Fig. 3) was of particular interest, since it was possible to measure the half-life of transfused red cells in his circulation. After the transfusion of 180 ml. of blood at the beginning of his first admission, his haemoglobin fell in eight days from 6.2 to 3.6 g./100 ml. (Fig. 3). Since this is a very quick breakdown we can assume that the destroyed red cells were mainly his own

cells containing haemoglobin S only; it is well known that sickle-cell-anaemia red cells have a very much shortened survival time. This child came to hospital with a haemoglobin of 2.8 g./100 ml. and lost 2.6 g./100 ml. in eight days. It is therefore reasonable to assume that when he was discharged after the first admission, having had two further blood transfusions, only an insignificant amount of his own red cells remained. In addition, his reticulocyte count during his first admission remained low with the exception of one small peak probably caused by the intravenous iron which was administered; there was also folic-acid deficiency, however, which prevented the reticulocyte response to iron being any higher or of longer duration.

Fifty-nine days after the last transfusion, when he was readmitted, the haemoglobin level had fallen to 6.3 g./100 ml., which shows the life-span of the transfused red cells to be approximately 120 days. Fig. 3 shows that the rate of disappearance of the transfused red cells (haemoglobin A) in the 26 days after readmission was not significantly different from that in the 59 days between admission. This was calculated from quantitation of electrophoretic strips on days 6 and 19 after the onset of folic-acid therapy, when respectively 35% haemoglobin S and 86% haemoglobin S were found. On the second occasion 5% haemoglobin F also was present, leaving about 10% haemoglobin A from the original transfused cells. From these findings it is clear that no extracorporeal defect producing an excessive destruction of normal cells was present in this case. Sprague and Paterson (1958) have suggested the possibility of such a mechanism in one case, but give no data to support it.

An unexpected finding in three cases (Nos. 3, 4, and 5) was the occurrence of an additional reticulocyte response with iron therapy (Fig. 6) (in Case 4 the iron was given first). In no case, however, was there any significant further increase in haemoglobin level. Presumably the increase in erythropoiesis was balanced by an increased rate of destruction.

Iron stains of sections of bone-marrow in all five cases were also interesting. Only in Case 1 was abundant iron present, but this infant had received a total of 550 ml. of blood, as well as a course of intramuscular iron, and in addition for two months had made scarcely any erythrocytes of his own. The reticulocyte response to folic-acid treatment in Case 1 cannot therefore have been in any way influenced by the simultaneous administration of oral iron. In Cases 4 and 5 a trace of iron was present in the marrow, but both these children had recently received blood transfusions. In Cases 2 and 3 no iron was detectable at all in the marrow. It would therefore seem that these four infants were deficient of iron as well as of folic acid. This is rather difficult to explain, since an increase in stainable iron in the marrow is usual in haemolytic anaemias. One can only suppose, therefore, that there was also a marked nutritional deficiency of iron in these cases. But in our experience such a deficiency is not usually striking in the straightforward megaloblastic anaemia of infancy. Iron therapy may be required in the course of recovery to produce sustained improvement, but any initial response to iron is negligible, and double reticulocyte responses when iron is given after folic-acid therapy have not been noted.

When patients with sickle-cell anaemia are seen with anaemia of a greater severity than is usual for this disease (as in our five patients) many investigators might

be inclined to ascribe the fall in haemoglobin to a haemolytic crisis. Such a haemolytic crisis must be distinguished from the aplastic crisis described by Singer *et al.* (1950) and from the painful crisis. The latter appears to be due to erythrocytosis from sickled red cells, and is commonly observed in bones, joints, and the abdomen (Golding *et al.*, 1959). Diggs (1956) has given good evidence that there is no increased destruction of red cells in the painful crisis, nor in any other acute episode related to sickle-cell anaemia. Our own experience seems to confirm this view: we have never observed a haemolytic crisis, and when we have seen an exacerbation of jaundice this has been accompanied neither by a fall in haemoglobin nor by a rise in reticulocyte count. Only once have we observed an aplastic crisis, and, in Jamaica at least, a "megaloblastic crisis" seems to be the major cause of such severely anaemic episodes in young children with sickle-cell anaemia.

Summary

In a series of 50 cases of megaloblastic anaemia of infancy five cases with associated sickle-cell anaemia were seen.

These cases presented with unusually low haemoglobin and reticulocyte levels for sickle-cell anaemia, and the bone-marrow was megaloblastic. Folic-acid therapy produced a dramatic increase in reticulocytes and a rise in haemoglobin to the level normally seen in sickle-cell anaemia. Some degree of associated iron deficiency was present in three cases.

In one of the cases described it was possible to measure the half-life of transfused erythrocytes with reasonable accuracy. The cell survival was found to be normal.

The question of crises in sickle-cell anaemia is discussed.

ADDENDUM.—Between November, 1959, and February, 1960, we have seen five more cases of sickle-cell disease with aplastic crises. Three of these were in one family in which a child with sickle-cell anaemia was affected. Three weeks later his sister with sickle-cell anaemia also had an aplastic crisis (Hb 1.8 g./100 ml.), and after another two weeks their mother, suffering from sickle-cell/haemoglobin C disease, had to be admitted with a combination of an aplastic and painful crisis.

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SPHEROCYTIC ANAEMIA, COMPLICATED BY MEGALOBlastic ANAEMIA OF PREGNANCY

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The association of congenital spherocytic anaemia (acholuric jaundice) with megaloblastic anaemia during pregnancy has been recorded by Davidson (1952), by Drury and Geoghegan (1957), and by Giles and Shuttleworth (1958). A further case with this association in two successive pregnancies is here reported.

Case History: First Pregnancy

A primipara aged 27 was admitted in labour as an emergency with toxæmia in the 40th week of pregnancy. She had previously enjoyed good health; there was no history of jaundice or any relevant family history. The pregnancy had proceeded normally—under regular medical supervision—until about two weeks before admission, when she became pale, easily tired, and short of breath; oedema of ankles, albuminuria, and an increase in blood-pressure were found.

On the day before admission the membranes had ruptured, discharging meconium-stained liquor. Examination showed pallor of the skin and mucous membranes and marked oedema of face, ankles, and abdomen. Cardio-vascular and respiratory systems were normal, with blood-pressure 150/75, pulse 92, and temperature 99° F. (37.2° C.). The urine contained a moderate amount of albumin. A healthy boy, weighing 7 lb. 15 oz. (3,600 g.), was born 12 hours after the onset of labour. The placenta was grossly infarcted; the membranes were complete. Blood loss was less than 1 pint (570 ml.).

A blood count after delivery was as follows: Hb, 4.4 g./100 ml. (30%); red cells 2,370,000; C.I., 0.65; white cells, 22,100 (polymorphonuclears 81%, lymphocytes 15% myelocytes 4%). The red blood cells were microcytic and hypochromic with marked anisocytosis and poikilocytosis; many showed polychromasia and punctate basophilia. There were eight normoblasts to 100 white blood cells.

Cultures of a catheter specimen of urine, and a high vaginal swab yielded a growth of coliform bacilli. After delivery blood-pressure was 130/70, pulse 128, and temperature 99.6° F. (37.6° C.) in the evening, which was not influenced by treatment with penicillin, sulphadimidine, or streptomycin. Three pints (1,700 ml.) of blood was transfused, but one week later a further count showed no great improvement. The white blood cells, however, had fallen to 2,850/c.mm.

Bone-marrow examination revealed a highly cellular marrow with many megaloblasts. A diagnosis of megaloblastic anaemia of pregnancy was made, and 100 mg. of folic acid was given by mouth for the first three days. Reticulocytes rose to 27% and the general condition improved. She was then transferred to a general hospital for further investigation. Clinical examination confirmed a grade I splenomegaly. Laboratory examinations showed increased corpuscular fragility and bilirubinaemia varying between 1 and 1.6 mg./100 ml.; other liver-function tests were essentially normal. Faecal fat excretion on a 50-g. daily intake over six days was normal, and free HCl was present in the gastric contents. Microspherocytes were