RESPONSE TO LETTUCE IN A PATIENT WITH MEGALOBLASTIC ANAEMIA ASSOCIATED WITH PREGNANCY

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Megaloblastic anaemia associated with pregnancy occurs frequently in the South African Bantu, and patients with severe anaemia usually present after pregnancy.1 The disease is associated with folate deficiency in that there is abnormally rapid clearance from the plasma of injected doses of folic acid,2 serum Lactobacillus casei folate values are subnormal,3 excessive amounts of formiminoglutamic acid are excreted in the urine after histidine loading,4 serum vitamin-B_{12} values are usually within normal limits,5, 6 and haematologic remission can be induced with small doses of synthetic folic acid (pteroylglutamic acid-PGA) but not small doses of vitamin B_{12}.7 Little is known, however, of the pathogenesis of this folate deficiency, although an association with malnutrition is often evident.8 If the deficiency is basically the result of inadequate folate in the diet, then provision of sufficient folate in the diet should effect cure. This paper reports the results of an attempt to induce haematologic remission with a diet supplemented with natural folate in the form of lettuce.

Methods

Standard haematological methods9 were used.

Serum vitamin-B_{12} was assayed by Lactobacillus leichmannii10 by Spray’s method,11 as elsewhere described.12 Serum L. casei folate activity was assayed by a method slightly modified from Herbert,13 Waters and Mollin,14 Formiminoglutamic acid (FIGLU) was measured by the combined enzymatic and spectrophotometric method of Chanarin and Bennett,15 in a 12-hour specimen of urine after oral administration of a 5-G histidine load. The absorption of folic acid was studied by measuring serum S. faecalis folic-acid activity and urinary radioactivity after a test dose of tritiated pteroylglutamic acid (\(^{3} \text{H} \) PGA). Normal values for these tests are as follows: Serum vitamin B_{12} = 250 - 1050 \( \mu \)g./ml.; serum L. casei folate activity = 6 - 20 \( \mu \)g./ml.; urinary FIGLU after 5 G histidine = 0 - 6 mg./12 hours; folic-acid absorption test—peak serum level >34 \( \mu \)g./ml.; urinary radioactivity >18% of administered dose of \(^{3} \text{H} \) PGA.

Case Report

A 28-year-old Sotho female was admitted to Baragwanath Hospital, Johannesburg, on 5 November 1962, complaining of weakness and swelling of the legs of 3 days’ duration. The patient had 3 children, the youngest of whom was 11 weeks old and was being breast fed. Delivery was apparently normal; there was no postpartum haemorrhage and the postnatal period was uneventful.

The patient’s home diet consisted of maize-meal porridge, milk (1 pint per day), potatoes, cabbage and ‘moroggo’ (dried leaves, mainly spinach). The cabbage and ‘moroggo’ were boiled for long periods in water until quite soft and the water discarded. No fish, eggs or meat were taken.

On examination the patient was extremely dyspnoeic with a pulse rate of 110/min. There was marked pallor of the conjunctivae, and the fundi showed haemorrhages and exudates. Pitting oedema of the hands, feet and face was present. The patient was unable to lie flat, and the jugular venous pressure was raised. A grade II systolic murmur was audible at the cardiac apex, and the liver was palpable 2 cm. below the costal margin. There were no clinical features of malnutrition.

The diagnosis on admission was anaemia with congestive cardiac failure.

Laboratory Findings

On admission the Hb was 3.2 G/100 ml., haematocrit 9%, MCHC 35%, reticulocytes 1.5%, leukocytes 6,500/cu.mm. (neutrophils 3,440, monocytes 65, lymphocytes 2,800, eosinophils 200). RBCs on the stained films were normochromic and showed marked anisopoikilocytosis, macrocytosis and ovalocytosis. Numerous hypersegmented neutrophils were present. Platelets appeared adequate. The bone marrow showed well-marked megaloblastic change. The vitamin-B_{12} concentration was 510 \( \mu \)g./ml. and serum L. casei folate activity 1.8 \( \mu \)g./ml. No urinary FIGLU was detected in a 12-hour urine specimen after administration of a 5G-histidine load.

Progress and Treatment

Treatment of the cardiac failure with ‘acycland’, ‘navidrex’ and ‘mersalyl’ was instituted. On the day following admission the patient remained extremely ill, with the Hb 2.4 G/100 ml. and a transfusion of the packed cells from 2 pints of blood was slowly administered. Following transfusion, the Hb rose to 6.0 G/100 ml. The signs of congestive failure diminished and the general condition improved.

The subsequent stages of treatment of the anaemia (Fig. 1) were as follows:

1. Control period. For a period of 7 days the patient received a diet which contained no green vegetables other than cabbage. The cabbage was boiled in a large volume of water, and the water discarded. On this diet no rise in reticulocyte count nor Hb was noted. Serum L. casei folate activity remained very low (0.8 \( \mu \)g./ml.) and there was excessive urinary FIGLU after histidine loading (88.6 mg./12 hours).

2. Lettuce extract. After the control period, therapy with lettuce was begun. For the trial to be valid an adequate quantity of lettuce had to be consumed. As fresh lettuce did not comprise a usual item of the patient’s diet, a liquid extract was tried. This was prepared by daily homogenizing fresh lettuce in a blender and filtering the expressed fluid. By this method of preparation, a large amount of lettuce pulp remained behind. Over a period of 7 days, 2,100 ml. of extract prepared from a total of 12 lettuces was administered by mouth. The extracts from different lettuces were assayed with L. casei for folate activity, both before and after treatment with chicken pancreas conjugase. The L. casei activity from 3 separate lettuce extracts was 0.8, 1.0 and 1.1 \( \mu \)g./ml., averaging 1.0 \( \mu \)g./ml. The patient thus received an average of 0.35 \( \mu \)g. of L. casei folate activity per day from the lettuce extract. On this therapy reticulocytes rose to 5% on the 6th day, but fell to 2% the next day, with no significant rise in Hb.

3. Whole lettuce. In view of the failure of the lettuce extract to produce a satisfactory reticulocyte response after 7 days, the patient was induced to eat 3 whole lettuces daily for a period of 6 days. A reticulocytosis of 14% occurred and the Hb and haematocrit values began to rise. The bone marrow after 6 days of whole lettuce therapy still showed megaloblastic change, but significantly less than on admission.

4. Pteroylglutamic acid. After 6 days of treatment with whole lettuce, 0.4 mg. of PGA was administered daily by mouth for a period of 10 days. This failed to induce a secondary reticulocyte response.

Following the therapeutic trial the patient received 15 mg. of PGA daily by intramuscular injection as the ‘saturating dose’. The folic acid level of the folate activity was in average of 6 HPGA was 66 \( \mu \)g./ml., and the urinary excretion of radioactivity was 41% of the administered dose. Both these results are within normal limits. When the Hb had reached 11.0 G/100 ml. the patient was...
discharged on a maintenance dose of PGA 5 mg daily. Eight weeks after admission the Hb was 14.1 G/100 ml.

DISCUSSION

The features in the present case are typical of the syndrome of severe megaloblastic anaemia following pregnancy. There can be no doubt of the folate deficiency in this patient in view of the very low serum L. casei folate activity, the excessive urinary FIGLU after repeated doses of histidine, and the normal serum vitamin-B12 level.

The difficulties of therapeutic trials in severely anaemic patients are well recognized. In the present case, initial blood transfusion raised the Hb to a level which enabled the patient to remain reasonably well, but not too high to mask haematological response. Nonetheless severe anaemia persisted during the early part of the trial, and test periods could not be prolonged for more than 7 days. There was no improvement in folate nutrition on a ward diet which contained no uncooked green vegetables. Supplementation with lettuce extract produced only a small, temporary rise in reticulocyte count. In view of the subsequent response when whole lettuce was administered, failure of the extract to induce a satisfactory reticulocyte response was probably related to its low folate content as a result of the method of preparation. The response following whole lettuce was not of the usual pattern which follows therapy with PGA, in that the reticulocyte peak was lower and more sustained, while the bone marrow still showed some megaloblastic change after 6 days of treatment. That the response was, however, close to optimal is suggested by the failure of PGA to produce a secondary reticulocyte response, although the sustained nature of the reticulocyte response may have been partly the result of the early institution of PGA treatment.

The demonstration that natural folate, in adequate amount, can induce haematologic response in a patient with megaloblastic anaemia following pregnancy is of interest in relation to the aetiology and prevention of the syndrome. Factors considered of possible aetologic importance in the folate deficiency associated with megaloblastic anaemia are well recognized. In the present case, initial blood transfusion raised the Hb to a level which enabled the patient to remain reasonably well, but not too high to mask haematological response. Nonetheless severe anaemia persisted during the early part of the trial, and test periods could not be prolonged for more than 7 days. There was no improvement in folate nutrition on a ward diet which contained no uncooked green vegetables. Supplementation with lettuce extract produced only a small, temporary rise in reticulocyte count. In view of the subsequent response when whole lettuce was administered, failure of the extract to induce a satisfactory reticulocyte response was probably related to its low folate content as a result of the method of preparation. The response following whole lettuce was not of the usual pattern which follows therapy with PGA, in that the reticulocyte peak was lower and more sustained, while the bone marrow still showed some megaloblastic change after 6 days of treatment. That the response was, however, close to optimal is suggested by the failure of PGA to produce a secondary reticulocyte response, although the sustained nature of the reticulocyte response may have been partly the result of the early institution of PGA treatment.

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blastic anaemia of pregnancy include interference with the utilization of folate, deficient dietary intake of folate, malabsorption of folate, and increased demand for folate produced by the developing foetus and by lactation. In patients who present with megaloblastic anaemia some months after delivery, interference with the utilization of folate during pregnancy is unlikely to be of importance. The absorption of folic acid, assessed by the serum S. faecalis levels after a test dose of PGA and urinary radioactivity after $^3$H PGA, is usually normal and haematologic response can be induced with small doses of PGA by mouth. However, response to small doses of PGA by mouth is not necessarily indicative of normal absorption of natural folate. Sheehy et al. noted response to small doses of PGA in patients with tropical sprue who had failed to respond to a diet containing more than 1 mg of 'folic acid-like activity' by assay. As the bulk of the folate activity in the diet is in the conjugated form. Sheehy et al. suggested that this natural material may be of little value to man. In the aetiology of megaloblastic anaemia following pregnancy, it is possible that conjugase activity and thus ability to absorb natural folate may be disturbed. However, the response to natural folate in the present patient makes a conjugase defect unlikely and suggests rather that the folate content of the diet is inadequate to induce haematologic remission. The finding also suggests that the syndrome can best be explained on the basis of deficient dietary folate intake associated with the increased demands for folate produced by pregnancy and lactation.

The consumption of adequate quantities of unpreserved green leafy vegetables, during pregnancy and lactation, appears of major importance in the prevention of megaloblastic anaemia.

**SUMMARY**

In a patient with megaloblastic anaemia following pregnancy, haematologic remission was induced by oral administration of natural folate in the form of lettuce. Subsequent administration of synthetic folic acid failed to induce a secondary reticulocyte response. The importance of dietary folate deficiency in the pathogenesis of this form of megaloblastic anaemia is emphasized.

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**REFERENCES**


**THE AETIOLOGY OF MILIARIA**


Prickly heat (miliaria rubra) is an important cause of morbidity in the gold mines of South Africa and there is evidence that its incidence is rising with the increase in deep-level mining and the hotter underground conditions in the Orange Free State. A similar high incidence is seen among deep-level coal miners in Australia. The disease itself may be relatively benign and the great majority of cases do not report sick with a single attack; but in the chronic case or when complications occur, usually eczematization and various forms of pyoderma, the problem assumes some importance.

Early in this investigation it became apparent that there are 2 distinct types of prickly heat:

1. A transient attack which occurs within 6 months of beginning work underground, or of transfer to a hotter or ill-ventilated section. This recovers spontaneously within a few weeks and may be regarded as an incident in the process of acclimatization; it affects the majority of men exposed to the necessary environment and is equivalent to the prickly heat experienced by many newcomers to the tropics. We refer to it as primary or acute miliaria.

2. Prickly heat developing in miners after years of freedom, sometimes without even an attack of primary

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