

Severe Nutritional Macrocytic Anemia in Emotionally Disturbed Patients

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MOST PHYSICIANS are cognizant of the symptom complex of syncope due to sudden blood loss or vasomotor phenomena resulting in acute cerebral ischemia, but few are aware of the frequency of the abnormalities attributed to the nervous system in chronic anemia. The psychiatric or neurologic aberration may result not only from tissue oxygen depression related to the severity of the anemia, but also to altered cellular metabolism of the central nervous system seen in certain anemias of nutritional origin.¹⁻² Conversely, emotionally disturbed patients may so alter their eating habits as to produce a deficiency state with resultant anemia.

In infants and children the most frequent deficiency state from which anemia may develop stems from inadequate intake of iron-containing foods. In adults iron-deficiency anemia occurs usually in women of the menstrual age group. This may be associated with abnormal blood loss in menses, pregnancy, or with dietary fads related to weight reduction. Chronic gastrointestinal bleeding is the most common cause of iron-deficiency anemia in

men. Very rare are the nutritional macrocytic anemias produced by inadequate intake or absorption of folic-acid-containing foods. The altered hematologic picture resembles pernicious anemia, but many clinical features including glossitis, the lack of neurologic complications, and the usual presence of free hydrochloric acid in the stomach juices allow the differentiation to be made with ease in most instances. This communication reports observation on five emotionally disturbed patients who developed nutritional macrocytic anemia.

CASE REPORTS

Case 1. D. P., a white female factory worker, aged 35 years, dated the onset of her illness two years previously. At that time full-mouth dental extractions were performed. Subsequent dentures which were ill-fitting proved unsatisfactory. The patient substituted milk for all solid food. She had eaten no meat for one year and for three months before admission had taken only milk and wine for nourishment. She had noted gradual onset of weakness; and for two months prior to admission had been forced to remain in bed because of exertional dyspnea, faintness, and palpitation. For two months she noted also painful sores in the mouth, puffiness of the face and ankles, and a thick, foul-smelling vaginal discharge with much vulvar irritation. Progressive mental depression and agitation developed in the six months before hospitalization.

Physical examination revealed a pale, bloated-appearing white woman who was markedly dyspneic on exertion. The temperature was 101° F., pulse, 100 per min, respirations, 20 per min, and weight, 135 lb. Pubic and axillary hair was sparse. Flame-shaped hemorrhages were seen in the retina on funduscopic

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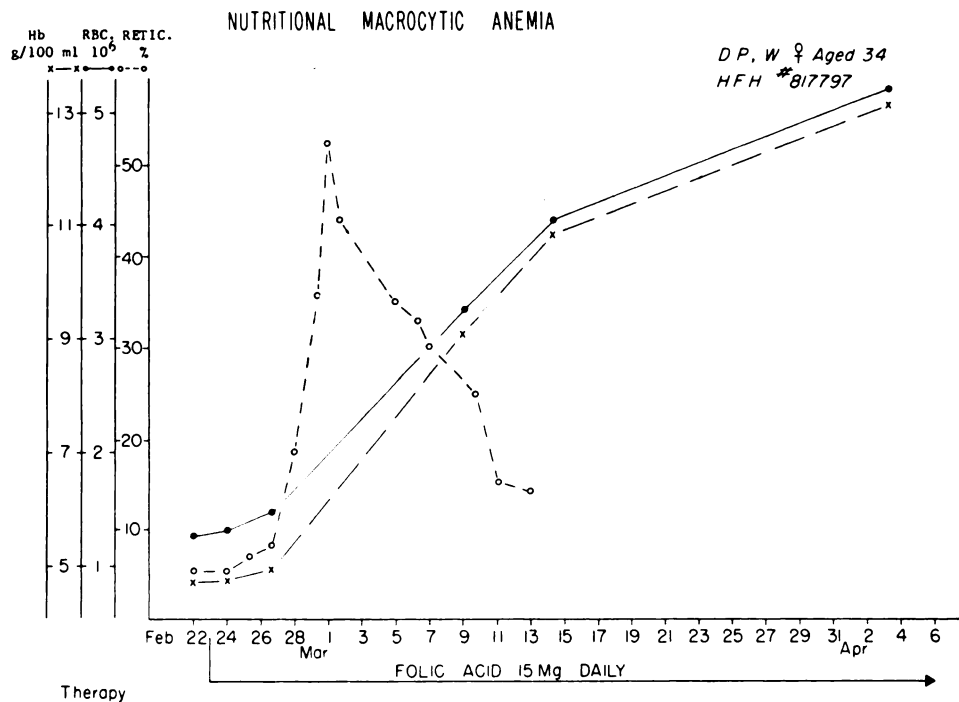


Fig. 1. Hematologic response to folic acid in nutritional macrocytic anemia.

examination. Many small, painful ulcers of the mucous membranes of the mouth and throat were evident. The teeth were absent. There was a generalized nontender lymph-adenopathy. About the ankles there were ecchymotic areas and a two-plus pitting edema. Vibratory and position senses were present. The vulva was red and swollen and a thick white vaginal discharge was noted.

On admission laboratory studies were reported as follows: hemoglobin, 5.7 g/ml; red blood count, 1.28 million/cu mm; white blood count, 3,750/cu mm. The blood smear demonstrated the erythrocytes to be macrocytic and several megaloblasts and many megalocytes were seen. The platelet count was 100,000/cu mm; reticulocyte count, 2.3 per cent; sedimentation rate, 0; hematocrit 9 mm. Urinalysis was normal. Blood nonprotein nitrogen, liver function tests, serum cholesterol levels, and van den Bergh tests were within normal limits. The blood albumin was 3.8 g/100 ml and globulin 1.6 g/100 ml. An oral glucose tolerance test was normal. Bone marrow smears revealed a hyperplastic picture with myeloid-erythroid ratio of 0.5:1. Megaloblasts and giant, developing hypersegmented neutrophils made up 64 per cent and 11.4 per cent respectively of the total blood cells. There was free hydrochloric acid in the stomach after histamine injection, and x-rays of the stomach, small bowel, and chest were within normal limits. Examination of the stool did not reveal blood or parasites. The blood vitamin A level was 25.6 mg/100 ml and vitamin

C level was 3 mg/100 ml, both values are within normal limits. The Schilling test revealed 15.8 per cent of tagged-vitamin B₁₂ in the urine.

The patient was treated with full diet and received folic acid 5 mg three times a day. Within four days the reticulocyte count was 19.8 per cent and reached a peak of 52.8 per cent in five days, slowly falling, thereafter, to 15.4 per cent on discharge three weeks after admission (Fig. 1).

She was seen one month later in the outpatient department and was completely asymptomatic. The hemoglobin now was 13.0/100 ml and erythrocytes 4.01 million/cu mm. During the interval of therapy marked improvement in the patient's irritability and confusion occurred.

Case 2. S. E., a white female, aged 38 years, sought medical care because of postprandial nausea and vomiting of one year's duration. During this interval her weight fell from 140 to 85 lb. Her diet at best consisted of one quart of milk with soggy crackers, one glass of orange juice a week, one half an egg a day. She would vomit a portion of this food each day. Her past history included a series of emotional problems, abnormal sexual practices, four marriages, alleged suicidal attempts, and a stint as an entertainer in night clubs of low repute.

On physical examination the patient was found to be agitated, emaciated, and she appeared much older than her stated age (Fig. 2). The mucous membranes of



Fig. 2. Case 2 (S. E.) demonstrating severe malnutrition with associated weight loss in an emotionally disturbed patient presenting a nutritional macrocytic anemia.

the mouth appeared mildly inflamed. The remainder of a general examination was negative but for vinyl implants in her breasts which presented an odd picture when viewed with her general cachexia. A psychiatric consultant classified her as demonstrating "psychophysiological gastrointestinal reactions."

On admission her hematologic status was as follows: hemoglobin 9.8 g/100 ml, erythrocytes 2.80 million/cu mm, leukocytes 5,700 per cu mm. The erythrocytes were macrocytic on the blood smear. The reticulocytes were 1.6 per cent, platelets 198,000/cu mm. Bone marrow aspiration demonstrated slightly increased cellularity and 7.4 per cent of the nucleated cells were megaloblasts. Blood sugar, nonprotein nitrogen, and serum proteins were within normal limits. Free hydrochloric acid was found on gastric analysis. In the Schilling test the patient excreted 12.8 per cent of the tagged vitamin B₁₂. Roentgenograms of the gastrointestinal tract and bones were normal.

In addition to sedatives and antispasmodics, the patient received an emulsified regular hospital diet by intestinal intubation. The reticulocytes rose to a maximum of 26 per cent on this regime. Management of the patient was extremely difficult because of her emotional problem. After two weeks of tube feeding the patient was discharged. Continuation of this therapy at home proved unsuccessful because of the patient's uncooperative attitude.

One month after intermittent hyperalimentation, the hemoglobin had risen to 11.5 g/100 ml and erythrocytes to 3.25 million/cu mm. In spite of our energetic measures she failed to continue her medical treatment and was lost to follow-up.

Case 3. T. S., a 39-year-old housewife, was first seen in December, 1949 for the treatment of neurodermatitis of ten years' duration. Her extreme nervousness was attributed to an intolerable home situation. She complained of anorexia, ate no fresh fruits or vegetables and very little meat. For two years prior to admission, the patient complained of a painful tongue, an unsteady gait, generalized skin tenderness, and parasthesias from the hips down.

The patient was in a depressed state. Her weight was 136 lb. Her skin presented numerous dry scaly reddened lesions up to two inches in diameter, most numerous on the arms, legs, and chest. The tongue was red and somewhat atrophic. Mild generalized lymphadenopathy was present. Liver, spleen, and kidneys were not palpable. Neurologic examination revealed a slight foot-drop over the left common peroneal nerve distribution, decreased vibratory sense, and an absent position sense in the toes. The Romberg test was positive, and she was generally hyporeflexic.

The initial laboratory studies were reported as follows: hemoglobin 11.4 g/100 ml, erythrocytes 2.94 million/cu mm, white blood cells 3,600/cu mm. The red cells were macrocytic, and the platelets numbered 160,000 per cu mm. The reticulocyte count was 1.2 per cent; the sedimentation rate, 28 mm in one hour; hematocrit, 35 mm. Urinalysis, cephalin-cholesterol, bromsulphalein, van den Bergh tests, serum albumin and globulin concentrations, and fasting blood sugar were normal. A bone marrow aspiration revealed a moderately cellular marrow with a myeloid-erythroid ratio of 5.8:1. Giant developing neutrophils and megaloblasts were present. An increased number of megakaryoblasts with poor formation of platelets was reported. The gastric analysis showed free hydrochloric acid 30 minutes after histamine, and an x-ray of the stomach was normal.

The patient was placed on a full diet, thiamine hydrochloride, and 15 mg folic acid daily. In two weeks the tongue was normal. When discharged six weeks after admission the neurologic signs had disappeared. She continued on the same diet with a supplement of folic acid 5 mg daily. When last seen seven weeks after her admission she was asymptomatic. The hemoglobin was 13.2 g/100 ml and erythrocytes 4.16 million per cu mm. The nervous tension was much reduced.

Case 4. C. B., a white female aged 35 years, complained of weakness, exertional dyspnea, and ankle edema. The patient's husband, a druggist, volunteered the information that his wife was addicted to narcotics and that for the preceding two years her diet had been inadequate. Breakfast consisted of one slice of toast and coffee; lunch and dinner (which she only

ate about three times a week) a tuna fish or, rarely, a chicken sandwich. The weight loss was estimated to be about 20 lb in the last year.

Physical examination revealed a pale woman whose weight was 104 lb; tongue was normal except for a few small vesicles at the anterior edge; thyroid was slightly enlarged, and small nontender lymph nodes were palpable in the neck, axilla, and inguinal regions. The lungs and heart were normal except for a grade II systolic nonradiating apical murmur; spleen, kidneys, and liver were not palpable. A two-plus ankle edema was noted.

The initial hematologic data were as follows: hemoglobin 6.0 g/100 ml, red blood count 1.05 million/cu mm, white blood cells 4,650 per cu mm with a normal differential count. The erythrocytes were macrocytic, and many megalocytes were noted on the blood smear. The platelets numbered 218,000/cu mm, and the reticulocyte count was 2.8 per cent. The sedimentation rate was 20 mm in one hour and hematocrit 22 mm. Urinalysis and blood nonprotein nitrogen were normal. Liver function studies which included cephalin-cholesterol, thymol turbidity, and flocculation as well as bromsulphalein were normal. The blood cholesterol was 174 mg/100 ml; van den Bergh, direct 0.07 mg/100 ml, total 0.30 mg/100 ml. Serum albumin 3.9/100 ml and globulin 1.5 g/100 ml. An

oral glucose tolerance curve was within normal limits, and a blood diastase was 60 per cent (normal = 50-150% Myer's method). Bone marrow aspiration revealed a hyperplastic marrow with a myeloid-erythroid ratio of 2:1. Numerous giant developing neutrophils and megaloblasts were seen. There was free acid in the stomach after histamine injection. X-ray study of the stomach and chest was normal. The stool fat was normal.

The patient was placed on a full diet and given 15 μ g of vitamin B₁₂ intramuscularly daily for two weeks. Five days after therapy was instituted the reticulocyte count rose to 15.3 per cent and after ten days of treatment reached a maximum of 30 per cent. The hemoglobin on discharge from the hospital was 8.8 g/100 ml. Associated with the improvement in the blood picture the patient's agitation and anxiety improved rapidly.

She was followed as an outpatient for two months. During this interval she received 5 mg of folic acid three times a day. When last observed, she was asymptomatic. The hemoglobin reached 14.1 g/100 ml and erythrocytes 4.54 million/cu mm.

Case 5. H. B., a 28-year-old white housewife, admitted to the hospital with the main complaint of weakness. She had been well until 18 months prior to admission at which time she had undergone great psychic trauma. Fuel oil which she had bought for a neighbor exploded, resulting in the death of five children. Many law suits followed. The patient became depressed and anorexic and for one year had eaten no meat or fruit. Her diet consisted mainly of milk and few vegetables. The patient's weight fell from 130 to 89 lb. She became progressively weaker and noted evening ankle edema. For four months before admission she had three to four soft brown stools daily and vomited when emotionally upset.

On physical examination she was found to be poorly nourished and pale, appearing much older than her stated age of 28 years (Fig. 3). Temperature 100.6° F., pulse 98 per min, weight 89 lb. Her skin was ashen, warm, and smooth. Fundoscopic examination revealed numerous flame-shaped and round hemorrhages along the course of the larger vessels near the disc. Her tongue was smooth and painful and there were many small superficial ulcers of the oral mucosa. The lungs were normal, and a grade III systolic murmur was described in the apical area. Liver, spleen, and kidneys were not palpable. Neurologic examination was negative. A few small ecchymotic areas were noted over the lower extremities.

Laboratory studies performed on admission were as follows: hemoglobin 2.7 g/100 ml, erythrocytes 750,000 million/cu mm, and macrocytic erythrocytes were seen on the blood smear. Platelets numbered 45,000 per cu mm, and the reticulocyte count was 1.8 per cent. A sedimentation rate was 3 mm in one hour, and hematocrit 10 mm. Urinalysis, blood nonprotein nitrogen, van den Bergh, and cephalin-cholesterol,

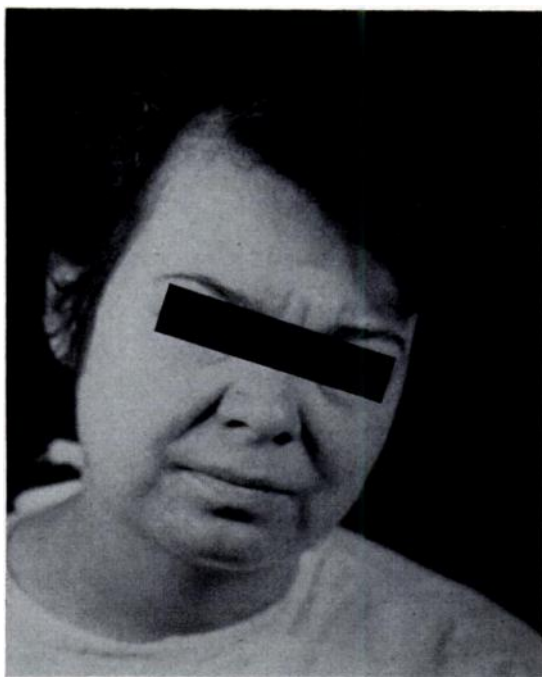


Fig. 3. Case 5 (H. B.) an emotionally depressed patient with nutritional macrocytic anemia. Puffiness of the face related to the anemia superficially obscures the recognition of severe underlying malnutrition.

bromsulphalein tests were normal. The serum albumin, globulin, and fasting blood sugar were normal. A bone marrow aspiration showed a myeloid erythroid ratio was 1.7:1, and the marrow was described as "so cellular the cells are arranged in sheets." There were 33 per cent giant developing neutrophils and 36 per cent megaloblasts. The gastric analysis revealed the presence of free acid on a fasting specimen, and an x-ray of the stomach and small bowel was normal. The stools were negative for ova, parasites, and blood.

The patient received 500 cc whole blood transfusion on admission. Thereafter, she was placed on a full diet, vitamins A and B, Brewer's yeast, refined liver extract 1 cc intramuscularly daily, and folic acid 10 mg three times a day. On this therapy her reticulocyte count rose in five days to 17.6 per cent and in two weeks to a peak of 23.6 per cent. On discharge her hemoglobin was 11.9 g/100 ml, and a bone marrow aspiration showed only slight increase in cellularity with a myeloid erythroid ratio of 2.2:1. Normoblastic regeneration was good, but there were a few scattered megaloblasts.

The patient was discharged on Brewer's yeast three times a day and on a full diet. When seen one month later she was asymptomatic, and her hemoglobin was 13.6 g/100 ml and erythrocytes 4.25 million/cu mm. Coincident with her hematologic improvement she became more alert with marked relief of her depression.

DISCUSSION

These cases have in common: young emotionally disturbed females, inadequate food intake, glossitis, severe macrocytic anemia, megaloblastic bone marrow, free hydrochloric acid in stomach juices without evidence of liver disease or gastrointestinal absorptive defect. Two patients responded adequately to folic acid, one to hyperalimentation, one to vitamin

B₁₂, and one to refined liver extract (Table I). It is of interest that in each instance all patients were lost to follow-up after a two-month period because of lack of cooperation. During the period of therapy the mental status improved remarkably only to relapse at a later date. Fragmentary information in three patients indicated a return of both nervous symptoms and the hematologic disturbances.

This group of patients undoubtedly represented states of multiple deficiencies indeed, Case 3 (T. S.) presented characteristic signs and symptoms of polyneuritis, presumably thiamine depletion.

The B-complex vitamins are essential for the maintenance of a normal central nervous system. For example, riboflavin deficiency produces no known hematologic or neurologic disease in man. Thiamine alterations may be associated with polyneuritis, nervousness, apathy, depressions, and parasthesias without significant changes of the blood.³ Lack of nicotinic acid is often followed by symptoms and signs of "dementia, dermatitis, and diarrhea." The failure of absorption of one μ g of vitamin B₁₂ daily by the gastrointestinal tracts results in a systemic combined degeneration of the cord and transient emotional instability.

Nutritional macrocytic anemia, nontropical and tropical sprue, and macrocytic anemia of pregnancy respond specifically to folic acid in a manner to suggest the anemia results from

TABLE I
Hematologic Results in the Treatment of Nutritional Macrocytic Anemia

Case	Pre-treatment			Therapy	Maximum reticulocytes, %	Post-treatment		Period of therapy
	Hb* g/100 ml	RBC million	Megalo- blasts bone marrow, %			Hb, g/100 ml	RBC million	
1. D. P.	5.7	1.28	64.0	15 mg folic acid q.d.	52.8	13.0	4.01	6 wk
2. S. E.	9.8	2.80	7.4	Tube feeding	26.0	11.5	3.25	1 mo
3. T. S.	11.4	2.94	4.8	15 mg folic acid q.d.	10.2	13.2	4.16	7 wk
4. C. B.	6.0	1.05	38.1	Vit. B ₁₂ 15 μ g q.d. I.M. for 2 wks, then 15 mg folic acid q.d.	30.0	14.1	4.54	2 mo
5. H. B.	2.7	0.75	36.0	500 cc whole blood; refined liver extract 1 cc I.M. q.d. for 2 wk, then 10 mg folic acid q.d.	23.6	13.6	4.25	2 mo

* Hb = hemoglobin; RBC = red blood cell count (millions/cu mm); q.d. = daily; I.M. = intramuscularly.

inadequate intake or absorption of this essential vitamin. The pathophysiology of the defect in these diseases is still not clear. Folic acid deficiency has been produced in dogs with resultant bone marrow hypoplasia, hypochromic anemia with mild microcytosis and glossitis. Megaloblastic anemia can be produced in monkeys by feeding milk diets deficient in ascorbic acid.⁴ Folic acid deficiency has been produced in pigs. The hematologic manifestations observed in these animals were (a) severe macrocytic anemia, (b) leukopenia, (c) thrombocytopenia, and (d) hyperplastic bone marrow with increase in immature nucleated red cells which resemble megaloblasts observed in pernicious anemia.⁵ On the basis of microbiologic data, the theory has been proposed that folic acid and vitamin B₁₂ act as coenzymes at different stages of nucleoprotein synthesis. An interruption of this process results in a megaloblastic picture in the bone marrow followed by a macrocytic anemia. (The mechanism of this disturbance has been discussed in detail by Mueller and Will.⁶)

CONCLUSIONS

Emotional instability may be associated with severe nutritional deficiency with resultant

macrocytic anemia. The anemia and altered cellular metabolism may augment the nervous symptoms.

The macrocytic anemia responds promptly to folic acid, vitamin B₁₂, refined liver extract, and hyperalimentation. The combination of folic acid and adequate supportive psychosomatic therapy offers the most favorable treatment.

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