

BRIEF REPORT

Pernicious Anemia with Neuropsychiatric Dysfunction in a Patient with Sickle Cell Anemia Treated with Folate Supplementation

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THE ADMINISTRATION OF FOLIC ACID CAN MASK THE MEGALOBLASTIC anemia caused by cobalamin deficiency.¹⁻⁵ More critically, this masking, although neither complete nor permanent,²⁻⁴ can permit neurologic dysfunction to develop and sometimes become irreversible.^{1-4,6} A few authors have proposed that folate may actually worsen the neurologic dysfunction.^{3,7}

Patients with sickle cell disease are often routinely given folate supplementation. The rationale is to prevent the deficiency caused by the increased folate turnover in chronic hemolytic anemia.⁸ However, clinical folate deficiency rarely occurs in patients with sickle cell disease, and objective evidence of a benefit from such supplementation is sparse.⁹ The use of folate supplementation is also based on the assumption that cobalamin deficiency almost never affects patients with sickle cell disease, therefore making folate treatment virtually risk-free.¹⁰ We describe a patient with sickle cell disease in whom neurologic deterioration due to untreated cobalamin deficiency developed during treatment with folate. Her case suggests that routine folate supplementation in patients with sickle cell disease should be approached with caution.

CASE REPORT

A 29-year-old black woman with sickle cell disease was evaluated in December 2001 for a worsening anemia that had resisted treatment for many months. She was noted to have an unsteady gait and mental changes.

Sickle cell anemia (homozygous for hemoglobin S) was diagnosed when the patient was eight years old, when she was found to be anemic. She received blood transfusions and had no sickle cell crises and received no further transfusions until she became pregnant in 1993 and again in 1995, by which time she had begun to take a folate supplement. During each of her pregnancies she had received a transfusion and prolonged treatment with oral iron. The base-line hemoglobin level was 8.1 g per deciliter, and the mean corpuscular volume was 103 μm^3 ; the serum cobalamin level was normal (221 ng per liter [163 pmol per liter]); and the lactate dehydrogenase level was slightly elevated (266 U per liter; normal range, 100 to 225 U per liter) in 1995.

The patient had no further crises or transfusions until January 2000, when she was hospitalized with a painful crisis; a mean corpuscular volume of 113 μm^3 appeared to have been overlooked. The hemoglobin level subsequently declined to as low as 5.4 g per deciliter, and she received transfusions. Iron and multivitamin therapy were added but had no noticeable effect. She was hospitalized with painful crises six more times during 2000 and 2001 and required repeated transfusions for low hemoglobin levels. Each time, folate was continued after her discharge. By November 2001, the lactate dehydrogenase level had increased to 2714 U per liter. Treatment for congestive heart failure was begun.

During an admission to another hospital in November 2001 for a painful crisis, the patient manifested confusion, impaired memory, and inappropriate behavior, consisting of public undressing, and her children went to live with relatives because they believed that she was "losing her mind." There was no previous history of psychiatric or neurologic dysfunction and no history of alcohol abuse.

Her evaluation in December 2001 demonstrated a strongly positive Romberg sign. All deep-tendon reflexes were slightly diminished, and proprioception seemed poor, but the patient's cooperation with the sensory examination was limited because of mental changes. She was irritable and had cognitive impairment.

An ankle injury due to a fall at home led to the patient's hospitalization in December 2001. The hemoglobin level was 5.4 g per deciliter, the white-cell count was 11,800 per cubic millimeter, the mean corpuscular volume was 104 μm^3 , the reticulocyte count was 281,000 per cubic millimeter, and the platelet count was 255,000 per cubic millimeter. The serum lactate dehydrogenase level was 2105 U per liter, and the total bilirubin level was 2.0 mg per deciliter. A computed tomographic scan of the brain showed no abnormalities. She was given a blood transfusion and hydroxyurea, which was quickly discontinued when the cause of her anemia and neurologic symptoms was uncovered.

Examination of peripheral-blood and bone marrow-aspirate smears showed megaloblastic anemia. The patient's serum cobalamin level was low (124 ng per liter [92 pmol per liter]; normal range, 211 to 911 ng per liter [156 to 672 pmol per liter]). The diagnosis of cobalamin deficiency was confirmed by a serum methylmalonic acid level that exceeded 10,000 nmol per liter (normal range, 30 to 279), measured by high-performance liquid chromatography (Quest Diagnostics) and a plasma total homocysteine level of 240 μmol per liter (normal range, 3.4 to 20.4), measured with an immunoassay (IM assay, performed by Quest Diagnostics). The serum creatinine and blood urea nitrogen levels were normal. As expected because of the patient's use of vitamin supplements, her serum folate level was elevated to more than 20 μg per liter (45.3 nmol per liter). The presence of antibodies to intrinsic factor in the blood and an elevated serum gastrin level (1062 ng per liter; normal value, less than 90) established the diagnosis of pernicious anemia. The results of thyroid-function tests were normal.

Folic acid supplements were discontinued, and

cobalamin injections (1000 μg), at first every few days and then weekly, were administered. The patient's memory began to improve within one week. After three months, her gait became normal and the Romberg sign disappeared. A dramatic change in her mental status revealed a pleasant, intelligent woman. After nine months of cobalamin treatment, the findings on neurologic and mental examination were normal. The hemoglobin level, mean corpuscular volume, and serum lactate dehydrogenase level have returned to base-line values. The plasma levels of homocysteine and methylmalonic acid are now normal. The patient receives monthly cobalamin injections and, for the past year, has had no painful crises or need for transfusions.

DISCUSSION

The characteristics of this case of pernicious anemia in a patient with sickle cell disease, as well as two other reported cases, are shown in Table 1.^{11,12} Pernicious anemia is not rare in blacks,^{13,14} and young black women are at particularly high risk.¹⁵ All three reported cases of pernicious anemia complicating sickle cell disease have been in young women. Periodic measurement of cobalamin levels may be advisable in patients with sickle cell disease who are routinely given folate supplementation. Moreover, superimposed cobalamin deficiency must be considered whenever anemia worsens or the mean corpuscular volume, lactate dehydrogenase level, or bilirubin level rises in a patient with sickle cell disease. In our patient, these changes were overlooked for nearly two years, perhaps because elevated bilirubin and lactate dehydrogenase levels and macrocytosis are nonspecific features of chronic hemolytic anemia.

The anemia in our patient, like that in the previous cases,^{11,12} worsened despite folate supplementation. Macrocytosis (masked more by transfusions than by folic acid), megaloblastic changes, and high lactate dehydrogenase levels persisted, and the need for transfusion continued. It is therefore clear that folate therapy does not entirely mask the anemia of cobalamin deficiency.²⁻⁴

The dramatic neuropsychiatric signs and symptoms in the case we describe underscore the concern that has been expressed about the adverse neurologic effects of giving folate without cobalamin to a patient with cobalamin deficiency. In this case, however, it is impossible to distinguish between a directly deleterious effect of folate therapy and the expect-

Table 1. Characteristics of Three Reported Cases of Sickle Cell Disease and Coexisting Pernicious Anemia. *

| Study | Folate Use | Neurologic and Psychiatric Findings | Hemoglobin | | Mean Corpuscular Volume | | Lactate Dehydrogenase | | Cobalamin | |
|----------------------------|------------|-------------------------------------|--------------|-------------------------|-------------------------|-------------------------|-----------------------|-------------------------|--------------|-------------------------|
| | | | At Diagnosis | After Cobalamin Therapy | At Diagnosis | After Cobalamin Therapy | At Diagnosis | After Cobalamin Therapy | At Diagnosis | After Cobalamin Therapy |
| | | | g/dl | | μm^3 | | U/liter | | ng/liter | |
| This study | Yes | Myelopathy, psychiatric symptoms | 3–4 | 7.2 | 113 | 104† | 2,714 | 273 | 124 | 530 |
| Sinow et al. ¹¹ | Yes | Psychiatric symptoms‡ | 8.9 | 9.3 | 107 | 103 | 465 | 195 | 107 | 275 |
| Chen et al. ¹² | Yes | None | 3.8 | 10.8 | 99 | 73 | 30,878 | — | 32 | — |

* Normal hemoglobin values range from 12.0 to 16.0 g per deciliter. Normal values for mean corpuscular volume range from 83 to 97 μm^3 . Normal values for lactate dehydrogenase range from 100 to 225 U per liter. Normal values for cobalamin range from 211 to 911 ng per liter. To convert values for cobalamin to picomoles per liter, multiply by 0.738. Some of the reference values are slightly different in the previously published reports.

† The value was probably modified by prior transfusion.

‡ The psychiatric dysfunction may have preceded the cobalamin deficiency.

ed progression of untreated cobalamin deficiency. Interestingly, the neuropsychiatric deterioration was reversible.

Although no conclusion is possible on the basis of one case, the contrast between the patient's seven painful crises while she had untreated cobalamin deficiency and her virtually crisis-free history before the deficiency developed and after it was corrected deserves mention. The temporal association raises the possibility that the hyperhomocysteinemia associated with long-standing cobalamin deficiency contributed to these crises. It has been proposed that mild hyperhomocysteinemia of unknown cause in sickle cell disease (reported median homocysteine values, 8.3 to 19.4 μmol per liter) may contribute to the vascular complications of the disorder.^{16–19} Our patient had severe hyperhomocysteinemia, which is common in pernicious anemia, in which levels

approach those seen in congenital homocystinuria.^{20–22} The hyperhomocysteinemia of cobalamin deficiency does not diminish when folic acid is given instead of cobalamin and persists even if the hemoglobin level rises.^{22,23}

We believe that the routine use of folate supplementation in patients with sickle cell disease, whose clinical benefit remains unproven, should be reconsidered. Routine use of cobalamin supplementation will not prevent the complications of superimposed pernicious anemia. If folic acid is given, periodic measurements of cobalamin levels seem advisable, and physicians must be alert to any changes in the blood count or clinical status that might represent early signs of cobalamin deficiency.

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