Clinical Utility of Folic Acid Testing for Patients with Anemia or Dementia

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BACKGROUND: Serum folic acid tests are routinely ordered by physicians for evaluating anemia and sometimes ordered for evaluating dementia and altered mental status.

OBJECTIVE: To determine the utility of routine folic acid testing for patients with anemia or dementia/ altered mental status in the era of folic acid fortification.

DESIGN: Retrospective analysis of consecutive folic acid tests performed on adults over a 4-month period; chart review of patients without anemia.

MEASUREMENTS AND MAIN RESULTS: Serum folic acid level, mean corpuscular volume (MCV), and hematocrit. We reviewed 1,007 folic acid tests performed on 980 patients. The average age was 63.8 years, and 62% of the tests were from outpatient facilities. Only 4 (0.4%) patients had folic acid levels <3 ng/mL, while 10 (1%) patients had levels of 3–4 ng/mL (borderline). Thirty-five percent of the folic acid tests were performed on patients who were not anemic; most of these were ordered to evaluate dementia or altered mental status and folic acid level was normal in all these patients. Only 7% of the patients tested had a macrocytic anemia; these patients were more likely than those without macrocytic anemia to have low folic acid levels (2.8% vs 0.4%, $p < .03$).

CONCLUSION: Low serum folic acid levels were rarely detected in a series of patients being evaluated for anemia, dementia, or altered mental status. The test should be reserved for patients with macrocytic anemia and those at high risk for folic acid deficiency.

KEY WORDS : folic acid, anemia, dementia.

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BACKGROUND

Folate is a water soluble vitamin, which is present in green, leafy vegetables, fruits, cereals and grains, nuts, and meats.¹ Folic acid, the synthetic form of folate used to fortify foods, has the same biologic effects as folate.^{1–3} The normal daily

requirement is 200–400 µg per day for unstressed individuals, and increases to 500–600 µg per day in pregnancy and lactation.^{4,5} Folic acid deficiency can produce megaloblastic anemia resulting in macrocytosis of red blood cells.⁶ During the perinatal period the deficiency is also associated with congenital neurological defects.⁷ Several studies have associated diets low in folic acid with increased risk of breast, pancreatic, and colon cancer.^{8–10} A low folic acid level has also been considered a risk factor for coronary artery disease.^{11–13}

The prevalence of folic acid deficiency varies in different parts of the world and depends on nutritional status, dietary habits, and the amount of alcohol consumption.^{14–17} In January of 1998, the Food and Drug Administration (FDA) mandated folic acid fortification of breakfast cereals and other foods.^{18,19} Before folic acid fortification, studies reported the prevalence of folic acid deficiency to be 3 to 4%.^{20,21} One study reported that the proportion of high-risk patients with low red cell folic acid levels declined from 4.8% in 1997 to 0.6% in 2004.²⁶

Serum folic acid tests are routinely ordered together with vitamin B12 levels in the assessment of anemia. In our institution, we also observed that folic acid were ordered together with B12 levels in assessing dementia and altered mental status, despite the fact that folic acid deficiency is not known to affect cognition.^{22,23}

We hypothesized that in the era of folic acid fortification of American diet, folic acid deficiency would be rare and, as a result, that routine folic acid testing for patients with anemia or dementia/ altered mental status would have minimal utility.

METHODS

We performed a retrospective review of all serum folic acid tests done at Baystate Medical Center in Springfield, Massachusetts during a 4-mo period. The central laboratory processes both inpatient specimens from the hospital and outpatient specimens from ambulatory practices in the surrounding community. The study protocol was approved by the institutional review board.

Flex software (The Flex Project, Berkeley, California)²⁴ was used to identify all folic acid tests done between May and August 2002. Our laboratory reported folic acid levels ≥ 3.0 ng/mL as normal. We categorized folic acid levels as low (<3.0 ng/mL), borderline (3.0 to 4.0 ng/mL) or normal (greater than 4.0 ng/mL). To assess physicians' reasons for ordering the test, we recorded any hemoglobin, hematocrit, mean corpuscular volume (MCV), vitamin B12 level, and thyroid stimulating hormone level in the 30 days before the folic acid being drawn; we subsequently reviewed the charts of all patients without anemia, defined as a

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hematocrit below 37% for a woman or 42% for a man. Macrocytosis was defined by a MCV >100 fL and microcytosis by a MCV <80 fL.

We also reviewed the medical records of patients with low or borderline folic acid levels to identify risk factors for folic acid deficiency and to note the physician's response in terms of further investigations or treatment. The proportions of patients with low folic acid with and without anemia, as well as with and without macrocytosis, were compared using Fisher's Exact Test.

RESULTS

During the study period, 1,007 folic acid tests were performed on 980 patients. Patients' characteristics and laboratory values are shown in Table 1. The average age was 63.8 years, with 44% of the patients over the age of 70. Overall, 588 (60%) patients were anemic, 71 (7.2%) patients had macrocytic and 53 (5.4%) patients had microcytic anemia. Thirty-five percent of folic acid tests were performed on patients without anemia and an additional 5% were done on patients without a recent hematocrit. Of these, 301 (74%) were performed to work up dementia or altered mental status. Four patients had folic acid levels <3.0 ng/mL (low) and 10 had levels between 3 ng/mL and 4 ng/mL (borderline). Levels below 3.0 ng/mL were equally likely among anemic and non-anemic patients (Table 2). Low folic acid levels were more common among patient with macrocytic anemia than among other patients (2.8% vs 0.2%, $p=.027$).

Elderly patients were no more likely to have low folic acid levels than younger patients. The majority of older patients had folic acid tests performed for dementia or altered mental status and all had folic acid levels >4 ng/mL. Of the 521 patients older than 65 years of age, only 3 had borderline levels and all were anemic. The 1 patient with a level <3.0 ng/mL had a macrocytic anemia.

All 14 patients with low or borderline folic acid levels were inpatients. None had a confirmatory red blood cell folic acid level or any further investigation at our institution into the cause of low folic acid. Clinically, 7 patients were at high risk for folic acid deficiency: 2 were alcoholic, 2 were on chemotherapy for advanced breast cancer, 1 had severe malabsorption following gastric bypass surgery, and 2 had poor oral intake. Out of 4 patients with low folic acid (<3 ng/mL) and anemia, 2 were macrocytic and 2 had normal MCV. Among patients with

Table 2. Low Folic Acid Levels According to Hemoglobin and Mean Corpuscular Volume

Hematocrit	MCV	Folic acid tests	Borderline low folic acid level (3–4 ng/mL)	Low folic acid level (<3 ng/mL)
	FI	N	N(%)	N(%)
Normal	80–100	279	1 (0.4)	1 (0.4)
	<80	31	0	0
	>100	40	0	0
	All	350	1 (0.3)	1 (0.3)
Anemia	80–100	478	5 (1.0)	1 (0.2)
	<80	53	1 (1.8)	0
	>100	71	2 (2.8)	2 (2.8)*
	All	602	8 (1.3)	3 (0.5)
Hematocrit not done		55	1 (1.8)	0

* $p=.038$, vs other anemic patients, $p=.027$, vs all patients. All other comparisons were non-significant.

MCV = mean corpuscular volume

macrocytic and low folic acid, 1 was on chronic hemodialysis and the other had advanced cancer. The risk factors for patients with normal MCV and low folic acid were alcohol abuse and poor oral intake. Five patients received folic acid replacement and 6 patients had a folic acid level rechecked within 12 months, at which time all levels had returned to normal.

DISCUSSION

This study demonstrates the low utility of routine folic acid testing in clinical practice. In our sample, folic acid deficiency was rare (0.4% of patients), and occurred primarily in patients with macrocytic anemia. Of the 14 patients with low or borderline levels, none had confirmatory red cell folic acid levels, only half received supplementation, and none had further testing to determine the etiology of the deficiency. Despite the lack of evidence that folic acid deficiency causes dementia or altered mental status, almost one third of all tests were done for this indication. None of these patients had folic acid deficiency.

In a study of adults, conducted before the mandatory fortification of cereals, Robinson et al. reported folic acid deficiency prevalence of 2.3%.²⁵ In a study of indigent patients, Joelson et al. found that 4.8% had low red cell folic acid levels in 1997, and that this prevalence fell to 0.6% in 2004 following the introduction of fortified foods.²⁶ The prefortification estimates are clearly higher than we observed, whereas our numbers were similar to those of Joelson et al. In fact, excluding those patients who had testing for altered cognition, 0.6% of our remaining patients had low folic acid levels. Joelson et al. also noted that most patients with low folic acid levels did not have macrocytosis. We found that half the patients with low folic acid levels had macrocytosis and that patients with macrocytic anemia were much more likely than other patients to have low folic acid levels. Finally, Robinson et al. observed that only 53% of the low levels were noted in the record and that folic acid was prescribed in only 24%. They concluded that folic acid supplementation rather than investigation was a safe and cost-effective approach.

Our results call into question the need for routine folic acid testing, especially for patients without macrocytic anemia and for those with dementia or altered mental status. Considering that over 1,000 tests lead to no significant clinical interventions,

Table 1. Patients' Characteristics and Laboratory Values

	No. (%; 95% CI)
Total folic acid tests	1007
Number of patients	980
Outpatient test	624 (62; 58–64)
Patients older than 70 yr	431 (44; 40–47)
Average age	64 ± 19.2 yrs
Female	608 (62; 58–65)
Mean folic acid (ng/mL)	16.8 ± 6.9
Patients with anemia	588 (60; 56–63)
Anemic patients with macrocytosis	71 (7.2; 5.7–9.0)
Anemic patients with microcytosis	53 (5.4; 4.1–7.0)
Tests for dementia or altered mental status	301 (30; 27–33)
Patients with folic acid levels <4 ng/mL	14 (1.4; 0.7–2.2)
Borderline low folic acid levels (3 to 4 ng/mL)	10 (1.0; 0.4–1.6)
Low folic acid levels (<3 ng/mL)	4 (0.4; 0.1–0.8)

it may be that folic acid testing can be suspended in all but a very few cases. Patients with alcohol abuse, malnutrition, malabsorption and those receiving chemotherapy remain at high risk for folic acid deficiency.

Our study has several limitations. First, we studied a single institution over one 4-month period. Our results may not be generalizable to other locations. Second, only serum folic acid levels were checked. Serum folic acid levels may be falsely normal after minimal intake of folic acid supplements or fortified food. Similarly, folic acid levels may be falsely low owing to heavy alcohol intake, anticonvulsant, or antineoplastic drugs.²⁷⁻²⁹ The red cell folic acid level is considered a better indicator of body stores³⁰ but was not used by clinicians at our hospital. However, at least 1 study found that, compared to serum folic acid levels, red cell folic acid levels do not provide additional clinical information in most patients.³¹ Nevertheless, whether the prevalence of folic acid deficiency was low, or our test was unable to detect it, the test was not useful.

In the era of fortification of the American diet, folic acid deficiency was rare among patients being evaluated for anemia or cognitive abnormalities. On the basis of these findings, folic acid testing should be reserved for patients with macrocytic anemia and those at high risk for folic acid deficiency. In light of the high proportion of folic acid testing done for dementia or altered mental status, educational interventions may be required to reduce the ordering of unnecessary folic acid levels.

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Conflict of Interest: None disclosed.

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