Pernicious anemia

Early identification to prevent permanent sequelae

Anand B. Karnad, MD Agnes Krozser-Hamati, MD

Preview

Because pernicious anemia is easily treated, early diagnosis is essential to prevent permanent neurologic deficits. Laboratory tests include a complete blood cell count, determination of the serum cobalamin level, and the Schilling test, in which radiolabeled vitamin B_{12} is used to demonstrate a lack of intrinsic factor. Therapy gives rapid relief but usually must be continued for life.

Pernicious anemia was uniformly fatal until 1934, when two Boston physicians, George Richards Minot and William Parry Murphy, were awarded the Nobel Prize in medicine for demonstrating the efficacy of a diet rich in liver for treating the disease. William Bosworth Castle's classic series of experiments at Boston City Hospital established that a lack of gastric intrinsic factor (due to achylia gastrica) was a hallmark of the disease. The vital ingredient in liver (extrinsic factor) was later shown to be vitamin B_{12} (cobalamin).

Characteristics

Adult-onset pernicious anemia is relatively common among persons of northern European descent who are older than age 50. (The annual incidence of new cases is 100/1 million population.) However, the disorder affects virtually all racial and ethnic groups and is slightly more common in women. A steep rise in incidence in older age-groups suggests that atrophic gastritis and pernicious anemia are a consequence of epithelial aging.[1]

With florid disease, manifestations consist of megaloblastic anemia, gastric atrophy followed by generalized epithelial atrophy, and neuropsychiatric abnormalities from subacute combined degeneration of the spinal cord and brain. The clinical expression of the disorder is variable; for example, progression of anemia may not parallel that of epithelial atrophy or neuropathy, and patients without anemia may have severe nervous system involvement. The reason for predominance of neurologic or hematologic dysfunction in individual patients remains uncertain.

MEGALOBLASTIC ANEMIA—The two distinctive deformities of blood cells in pernicious anemia are (1) hypersegmentation of neutrophils and (2) macro-ovalocytosis (the presence of large, egg-shaped red cells, or macro-ovalocytes). Although the volume of macro-ovalocytes is about twice normal, red cells vary in size and shape, so the average mean corpuscular volume in patients with severe anemia falls in the range of 110 to 140 fL. Severe anemia may be accompanied by moderate leukopenia and, less often, by severe thrombocytopenia. Morphologic characteristics of the bone marrow include marked nuclear-cytoplasmic dyssynchrony in both erythroid and myeloid cells; the nuclear chromatin acquires an unevenly speckled pattern that gives it a "sliced salami" appearance.[2]

GASTRIC ATROPHY—Atrophy of the gastric mucosa, which is the initial lesion of pernicious anemia, affects the proximal two thirds of the stomach. Endoscopic biopsy reveals a thin mucosa with sparse glands surrounded by infiltrates of lymphocytes and plasma cells. Because cobalamin deficiency affects all exfoliating cell populations, atrophy of the tongue, lips, skin, and enteric and vaginal mucosa may be seen.

NEUROPSYCHIATRIC ABNORMALITIES—Subacute combined degeneration of the spinal cord and brain is the characteristic neuropathic disorder caused by cobalamin deficiency. Symmetric wasting of hands and feet and loss of vibration sense in the lower extremities are caused by patchy demyelination of the dorsal and lateral columns of the spinal cord. In cases of severe untreated cobalamin deficiency, optic neuropathies and central nervous system abnor-

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Table 1. Causes of macrocytosis*

Megaloblastic
Vitamin B_{12} deficiency
Folic acid deficiency

Normoblastic
Alcohol
Reticulocytosis
Myelodysplastic syndromes
Hypothyroidism
Chronic liver disease
Anticancer drugs (eg, hydroxyurea [Hydrea])

*Mean corpuscular volume > 94 fL.

Table 2. Causes of low serum cobalamin levels in the presence of normal tissue stores of vitamin B_{12}

Normal pregnancy
Partial gastrectomy
Folate deficiency
Iron deficiency
Severe atrophic gastritis
Strict vegetarianism

Table 3. Schilling test values in pernicious anemia and malabsorption syndromes with and without administration of intrinsic factor

	Urinary excretion of radiolabeled vitamin B_{12} (%)	
	Without IF	With IF
Normal	≥8	≥8
Pernicious anemia	<8	≥8
Malabsorption	<8	<8
Food-bound malabsorption	≥8	≥8

IF, intrinsic factor.

malities ranging from confusion to dementia may be seen.

Recent studies[3,4] indicate that neurologic disorders encountered in current clinical practice are less severe than in the past and are highly responsive to therapy. Healton and associates,[3] describing their experience with neurologic disorders in 143 patients seen over a 17-year period at two New York hospitals, found that pernicious anemia was the most common underlying cause of the cobalamin deficiency. The most frequent symptoms were paresthesias and ataxia, whereas the most common objective findings were diminished vibratory sensation and proprioception in the lower extremities. A variety of other symptoms and signs were seen, including muscle weakness, diminished reflexes, spasticity, urinary and fecal incontinence, orthostatic hypotension, dementia, psychoses, and mood disturbances. Multiple neurologic syndromes were seen in a single patient.

The hematocrit was normal in 27% of the patients, and the mean corpuscular volume was normal in 23%. In most of the patients, careful review of blood smears and bone marrow aspirates revealed subtle morphologic evidence of megaloblastic changes. All patients responded to cobalamin therapy, and recovery was complete in 47%. The scope of neurologic residua after treatment was strongly related to the extent and duration of symptoms before therapy.

Laboratory diagnosis

A complete blood cell count, determination of the serum cobalamin level, and the Schilling test aid in the diagnosis of pernicious anemia.

The Schilling test can be used to demonstrate a lack of intrinsic factor and confirm the diagnosis of pernicious anemia.

COMPLETE BLOOD COUNT—Macrocytosis may be the first sign of the disease; however, the differential diagnosis of macrocytosis is extensive (table 1). The appearance of the blood film is of little help in early cases, and the white blood cell and platelet counts do not change until anemia is severe.

In the absence of changes in the blood, examination of bone marrow aspirate is the only other way of identifying megaloblastosis. When megaloblastic changes are confirmed, the patient is categorized as having megaloblastic rather than normoblastic macrocytosis.[5]

SERUM COBALAMIN LEVEL—All patients who have cobalamin deficiency have a low serum vitamin B_{12} level, although cobalamin deficiency is not the only cause. Low serum cobalamin levels in the presence of normal vitamin B_{12} tissue stores (false-positives) are common (table 2). The serum vitamin B_{12} level is just one piece of evidence that needs to be fitted into the rest of the clinical picture. The presence of megaloblastic hematopoiesis accompanied by a low serum vitamin B_{12} level is not sufficient proof of pernicious anemia; lack of gastric intrinsic factor must be established as the cause of these changes.[5]

SCHILLING TEST—This absorption test uses radiolabeled vitamin B_{12} to show that lack of intrinsic factor is the cause of a low serum cobalamin level. Impaired absorption of vitamin B_{12} that is corrected by repeating the test with added intrinsic factor (table 3) implies a lack of intrinsic factor and confirms the diagnosis of pernicious anemia. The test is usually done by measuring radioactivity in a 24-hour urine specimen, and incomplete collection of urine (especially in a very elderly patient) may cause a false-positive or false-negative result; this is more common in outpatients than inpatients. Measurement of plasma radioactivity 8 to 10 minutes after the start of the Schilling test has been found to be as reliable as measurement in a complete urine specimen.[5]

A normal result on the Schilling test in patients with a low serum cobalamin level indicates food-bound cobalamin malabsorption. This condition has stimulated the widespread use of a "food" Schilling test (or egg-yolk cobalamin absorption test), in which the ingested cobalamin is derived from eggs produced by hens injected with radiolabeled cobalamin. Malabsorption of food-bound cobalamin can cause a variety of neuro-

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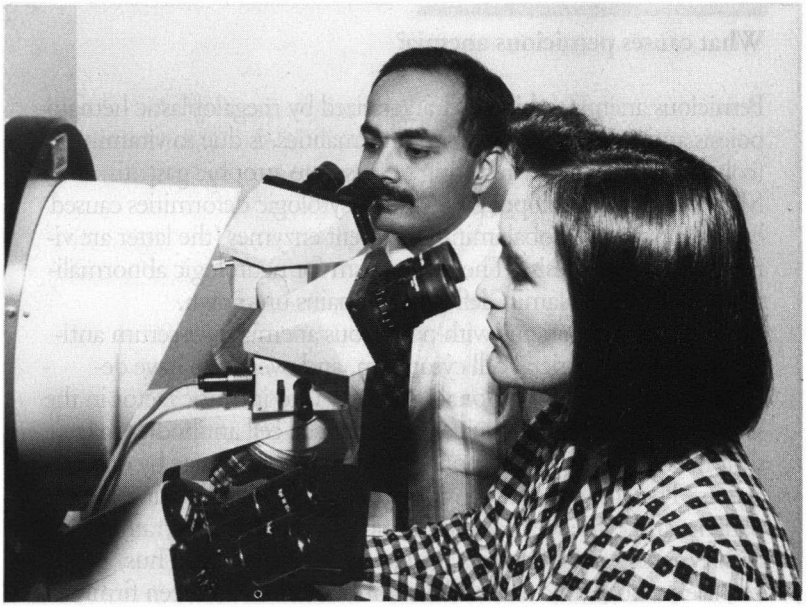
What causes pernicious anemia?

Pernicious anemia, which is characterized by megaloblastic hematopoiesis and/or neuropsychiatric abnormalities, is due to vitamin B_{12} (cobalamin) deficiency resulting from severe atrophic gastritis. Megaloblastic hematopoiesis is due to cytologic deformities caused by malfunction of cobalamin-dependent enzymes (the latter are vital for DNA synthesis). The mechanism for neurologic abnormalities seen with cobalamin deficiency remains unknown.

Over 90% of patients with pernicious anemia have serum antibodies (IgG) to parietal cell cytoplasm, and over 75% have detectable antibodies (polyclonal IgG or IgA) to intrinsic factor in the serum, saliva, and gastric juice. Anti–parietal cell antibodies may simply be evidence of a response to parietal cell damage by other agents. The absence of intrinsic factor antibodies in about 25% of patients and evidence that these antibodies appear after, rather than before, gastric atrophy argue against an initiating role. Thus, as yet, the pathogenetic role of these antibodies has not been firmly established.

Oral cobalamin is available to treat patients with pernicious anemia, but the lowest effective dose has not been established.



Anand B. Karnad, MD
Agnes Krozser-Hamati, MD
Drs Karnad (left) and Krozser-Hamati (right) are assistant professors of medicine, division of hematology-oncology, department of internal medicine, James H. Quillen College of Medicine, East Tennessee State University, Johnson City. The division focuses on clinical research in hematologic abnormalities in elderly patients, with a strong emphasis on geriatric oncology.

psychiatric manifestations; therefore, low cobalamin levels in the presence of normal results on the Schilling test should not be dismissed without performing a test for malabsorption of food-bound cobalamin.[6]

Treatment

In treating pernicious anemia, the basic regimen of first administering parenteral cyanocobalamin at a slow rate to replenish reserves and then administering 1,000 μg intramuscularly in monthly maintenance doses for life is well known. The optimal dose and frequency of maintenance therapy are not yet well established. There is no evidence that hydroxycobalamin (AlphaRedisol) is superior to cyanocobalamin.

Oral cobalamin is available and has been shown to be effective (large doses are absorbed independently of intrinsic factor); however, present data are not sufficient to establish the lowest effective oral dose for the majority of patients.[7,8] Patients receiving oral cobalamin therapy should be closely monitored.

The hematologic response to therapy is rapid, with brisk reticulocytosis that reaches a peak 5 to 6 days after initiation of therapy. In the patients observed by Healton and associates,[3] some evidence of response was always seen during the first 3 months of treatment. As noted, in patients with neurologic syndromes, the amount of improvement over baseline neurologic status is inversely related to both hematocrit level and duration of symptoms.

Summary

Pernicious anemia can be confidently diagnosed in a patient who has megaloblastic hematopoiesis, low serum cobalamin level, and impaired vitamin B_{12} absorption correctable by administering intrinsic factor. Recent studies suggest that neurologic disorders in patients with pernicious anemia are less severe than in the past, highly respon-

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sive to therapy, and seen in the absence of anemia and macrocytosis. A low serum cobalamin level in the absence of anemia, particularly in a patient with a neurologic disorder, should not be ignored. PGM

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Address for correspondence: Anand B. Karnad, MD, Division of Hematology-Oncology, Department of Internal Medicine, PO Box 70622, James H. Quillen College of Medicine, East Tennessee State University, Johnson City, TN 37614-0622.

References

1. **Jandl JH.** Blood: textbook of hematology. Boston: Little, Brown, 1987:161
2. **Jandl JH.** Blood: pathophysiology. St Louis: Mosby–Year Book, 1991:108
3. **Healton EB, Savage DG, Brust JC, et al.** Neurologic aspects of cobalamin deficiency. Medicine 1991;70(4):229-45
4. **Beck WS.** Neuropsychiatric consequences of cobalamin deficiency. Adv Intern Med 1991;36: 33-56
5. **Chanarin I.** How to diagnose (and not misdiagnose) pernicious anaemia. Blood Rev 1987; 1(4):280-3
6. **Carmel R, Sinow RM, Siegel ME, et al.** Food cobalamin malabsorption occurs frequently in patients with unexplained low serum cobalamin levels. Arch Intern Med 1988;148(8):1715-9
7. **Lederle FA.** Oral cobalamin for pernicious anemia: medicine's best kept secret? JAMA 1991;265(1):94-5
8. **Hathcock JN, Troendle GJ.** Oral cobalamin for treatment of pernicious anemia. (Editorial) JAMA 1991;265(1):96-7