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EASILY MISSED?

Pernicious anaemia

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What you need to know

- Consider pernicious anaemia in patients complaining of unexplained fatigue, memory loss, poor concentration, or paraesthesia
- About a third of patients may have normal B12 levels and normocytic anaemia, leading to a missed or delayed diagnosis
- Screening tests for patients with suspected pernicious anaemia should include full blood count and serum cobalamin assay
- Prompt treatment with B12 supplementation usually reverses anaemia and neurological symptoms, and patients will require lifelong B12 supplementation

A 55 year old woman presents to her GP with fatigue, "pins and needles" sensation in her feet, and poor concentration. Clinical examination and routine blood investigations were unremarkable. Her symptoms gradually worsened over two years. She also developed exertional dyspnoea and unsteadiness while walking. On examination, she had pallor, resting tachycardia, and sensory neuropathy in both legs. A peripheral blood smear revealed macrocytic anaemia and hypersegmented neutrophils. Further investigations confirmed severe B12 deficiency secondary to pernicious anaemia.

What is pernicious anaemia?

Pernicious anaemia is an autoimmune disorder affecting the gastric mucosa with impaired absorption of dietary cobalamin (vitamin B12) resulting in B12 deficiency. Figure 1 depicts the pathophysiology of pernicious anaemia. Vitamin B12 is essential for production of blood cells and myelination of nerves. Its deficiency causes megaloblastic anaemia. Neuronal demyelination and subsequent degeneration lead to neurological and neuropsychiatric manifestations.[1]

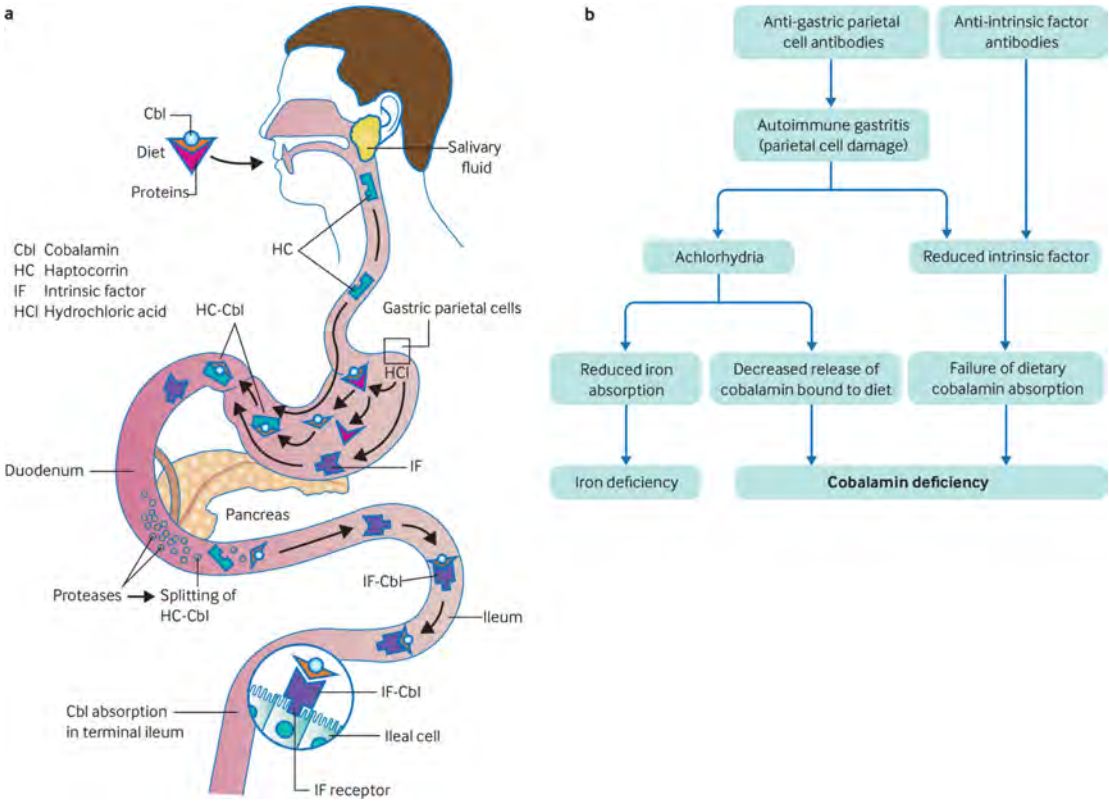

Fig 1 | (a) Normal process of dietary cobalamin absorption, and (b) the pathophysiology of pernicious anaemia

This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, professor of primary care, Department of Primary Care Health Sciences, University of Oxford, and Dr Kevin Barraclough, School of Social and Community Medicine, University of Bristol. You can read more about how to prepare and submit an Education article on our Instructions for Authors pages: https://www.bmj.com/about-bmj/resources-authors/article-types

How common is it?

Pernicious anaemia is relatively rare. Between 50 and 200 per 100 000 people in the UK and 150 per 100 000 people in the US are affected.[2] It can affect all age groups, but is seen more commonly in adults over 70 years old.[1] Because of its association with autoimmune disorders such as autoimmune thyroiditis, Addison's disease, vitiligo, and type 1 diabetes, a personal or family history of these conditions increases the likelihood of pernicious anaemia.[3 4]

Why is it missed?

Symptoms manifest insidiously and rarely raise clinical suspicion.[3] Box 1 lists symptoms of pernicious anaemia. These are often present in other conditions as well, leading to a missed or delayed diagnosis.

Box 1: Common clinical features of pernicious anaemia[5]

General symptoms

- Tiredness
- Dry skin
- Brittle nails
- Glossitis
- Hair loss or greying

Neurological symptoms

- Memory loss
- Poor concentration
- Clumsiness
- "Pins and needles" sensation
- Poor sleep
- Confusion
- Dizziness
- Nominal aphasia
- Balance problems

Cardio-respiratory symptoms

- Shortness of breath
- Palpitations

Gastrointestinal problems

- Diarrhoea
- Indigestion
- Stomach cramps
- Loss of appetite
- Loss of taste

Emotional symptoms

- Irritability
- Impatience
- Mood swings
- Suicidal thoughts

Tiredness, memory loss, and poor concentration were the most common symptoms reported in an online survey of 889 patients with pernicious anaemia in the UK. Of these patients, 30-45% reported having a delayed diagnosis beyond one year, and up to 10 years, or being initially misdiagnosed with conditions such as depression, chronic fatigue syndrome, hypothyroidism, multiple sclerosis, fibromyalgia, and diabetes.[5] Some patients present with gastrointestinal symptoms such as dyspepsia before development of anaemia.[6]

Limitations in accuracy of diagnostic tests and variability in findings present further diagnostic difficulties.[7] About a quarter of patients have neurological symptoms without anaemia and macrocytosis.[4] Rarely, patients may have symptoms with normal serum cobalamin levels.[8] Achlorhydria secondary to atrophic gastritis can impair iron absorption. About 20% of patients with pernicious anaemia have coexisting iron deficiency, and the blood film may reveal normocytic anaemia, or even microcytic anaemia in extreme circumstances, masking the diagnosis of B12 deficiency.[8]

Why does it matter?

Patients can develop complications of B12 deficiency if not diagnosed and treated early.[1 3] There have been case reports of heart failure due to severe anaemia.[9] It is uncertain how common haematological and neurological complications are in pernicious anaemia.

Peripheral neuropathy is an early neurological manifestation of pernicious anaemia, which causes reversible paraesthesia and numbness. Subacute combined degeneration of the spinal cord occurs in later stages. This can lead to weakness of the limbs and trunk, ataxia, visual defects, and autonomic dysfunction.[10] In a review of observational studies, 75% of patients (43/57) with subacute combined degeneration of the spinal cord had pernicious anaemia. Early diagnosis and treatment improve chances of recovery: 14% (8/57) of patients had complete neurological recovery after cobalamin treatment, and the remainder had some improvement in symptoms. The median duration of symptoms at diagnosis was six weeks (range 2-24 weeks) in those who had complete recovery, and 12 weeks (range 1-84) in patients with partial recovery.[11] Neuropsychiatric manifestations such as depression, psychosis, cognitive impairment, and obsessive compulsive disorder can occur, as per case reports of patients with pernicious anaemia.[12]

Very rarely, infants of mothers with undiagnosed pernicious anaemia can develop cobalamin deficiency leading to developmental delay and learning difficulties, as seen in a few case reports.[13]

Patients with pernicious anaemia are at an increased risk of non-cardia gastric cancers and gastric carcinoid tumours. In an analysis of 843 patients with pernicious anaemia from multiple cohort studies, 6.9% of patients (58/843) developed gastric cancer over a follow-up of 11 years.[14] A missed diagnoses of pernicious anaemia can delay detection of precancerous changes and lead to poor outcomes.

How is pernicious anaemia diagnosed?

Clinical

A high index of clinical suspicion and awareness of the red flags (table 1) are essential for a timely diagnosis. Obtain a detailed history in view of the varied symptoms of pernicious anaemia (box 1). Encourage patients or their carers to make a list of all the symptoms experienced over a period.

Table 1 | Red flags for complications of pernicious anaemia

Symptoms and signs	Complications
Paraesthesia Hyporeflexia	Peripheral neuropathy
Ataxic gait Reduced muscle power	Subacute combined degeneration of the spinal cord
Shortness of breath Peripheral oedema	Cardiac failure
Cognitive impairment Depression	Neuropsychiatric manifestation

Exclude other causes of B12 deficiency such as vegan diet, a history of ileal disease or resection, and total or partial gastrectomy.

Investigations

Request a full blood count and a blood film. Elevated red blood cell mean corpuscular volume (macrocytosis) and hypersegmented neutrophils point towards cobalamin deficiency (fig 2). About a third of patients with B12 deficiency may not have macrocytosis. Macrocytosis can also occur with folate deficiency, liver disease and alcoholism.[4 8] Figure 3 presents an algorithm for investigating patients with suspected pernicious anaemia.

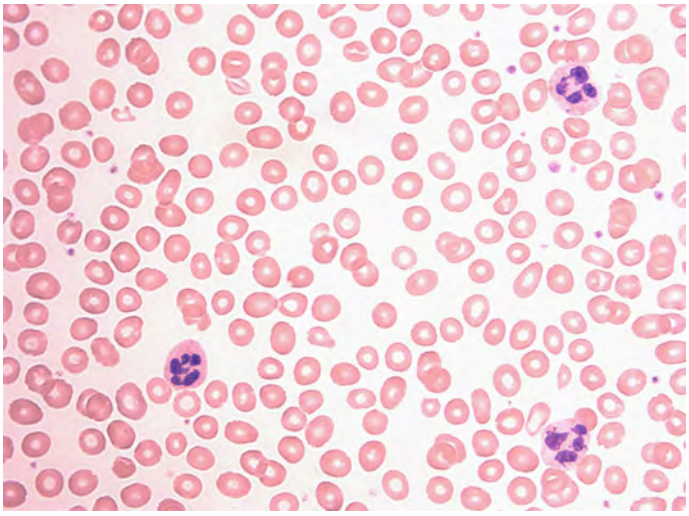

Fig 2 | Blood film in a patient with pernicious anaemia showing the presence of macro-ovalocytes and hypersegmented neutrophils

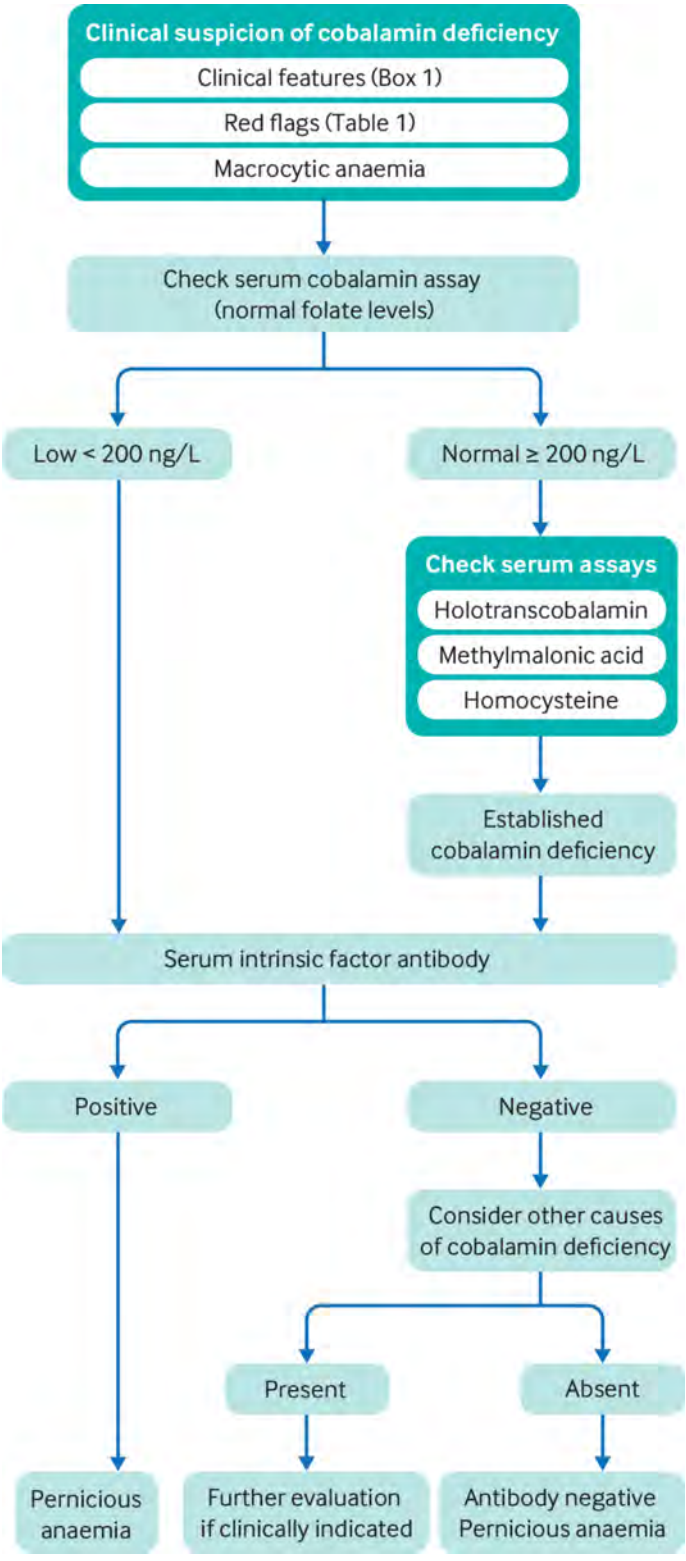

Fig 3 | Algorithm for investigating suspected pernicious anaemia

Test for serum vitamin B12 and folate levels in patients with suspected clinical symptoms, and those with anaemia, particularly if macrocytic.[3 7] Serum cobalamin assay is not expensive and is useful for initial evaluation (sensitivity 97% at serum cobalamin levels <200 ng/L). Its levels can be affected by diet, folate deficiency,

pregnancy, oral contraceptives, HIV infection, and metformin. Further tests for B12 deficiency such as holotranscobalamin, methylmalonic acid, and homocysteine are usually performed in secondary care when there is clinical suspicion of cobalamin deficiency but patients have borderline or normal serum cobalamin values.[7 8]

There is no "gold standard" test for pernicious anaemia and lack of quality evidence regarding the diagnostic accuracy of tests.[15] Antibodies to intrinsic factor are highly specific (95-100%) for pernicious anaemia, but a negative result does not rule out the disease due to the test's low sensitivity (50-60%).[7 8] Testing for anti-gastric parietal cell antibodies is not recommended because of the variable specificity of 50-100%.[4]

How is pernicious anaemia managed?

Patients with pernicious anaemia require lifelong cobalamin supplementation. Intramuscular vitamin B12 injections are typically recommended. Box 2 lists the treatment regimen recommended by the British National Formulary.[16]

Box 2: Treatment regimen for vitamin B12 deficiency[16]

- Lifelong supplementation with vitamin B12 is needed in pernicious anaemia

No neurological symptoms

- Intramuscular injection of hydroxocobalamin (1000 µg) thrice a week for two weeks
- *Maintenance dose*—Intramuscular injection once every three months

Neurological symptoms

- Alternate day intramuscular injections of hydroxocobalamin until maximal improvement is noted clinically
- *Maintenance dose*—Intramuscular injection once every two months

Oral cobalamin therapy with high dose (1000-2000 µg) pills taken daily is shown to have similar efficacy in improving symptoms and haematological parameters of B12 deficiency in small studies. However, it is not preferred for initial treatment of patients with severe symptoms because of the possibility of slower response compared with intramuscular injection.[1 4 15 17] Oral therapy may be used for long term maintenance treatment.[4] Adherence to daily treatment and dosing with meals may present a challenge for some patients. High dose oral formulations are available at UK pharmacies, but not available in several countries.

With adequate cobalamin replacement, reticulocyte count generally increases and peaks at one week, and anaemia and macrocytosis normalise within eight weeks. Neurological improvement is usually slower and not as predictable.[15] Patients may have a variable course of recovery of symptoms. The degree of neurological recovery is observed to be inversely proportional to the severity and duration of neurological symptoms before cobalamin treatment.[10]

Since patients may discontinue treatment when they feel better, it is important to discuss the need for lifelong cobalamin supplementation and regular monitoring of B12 levels, and about the likely course of recovery. It should be recognised that adherence to long term treatment can be a challenge and hence a management plan considering the patient's preferences and context should be developed.[15]

Gastroscopy is recommended initially in patients diagnosed with pernicious anaemia for the diagnosis of atrophic gastritis and for evaluation of gastric malignancies.[1 4] Offer referral to a gastroenterologist.

Education into practice

- Based on reading this article, how will you diagnose pernicious anaemia early?
- How will you discuss with your patients about their views on convenience and compliance of daily cobalamin tablets versus three-monthly injections for lifelong supplementation?

How patients were involved in the creation of this article

One of our patients struggled with multiple symptoms from anaemia and peripheral neuropathy for years before being diagnosed with pernicious anaemia. At a recent appointment, she discussed her life before and after the diagnosis of pernicious anaemia and how her symptoms started to improve dramatically after the first cobalamin injection. She also read our manuscript in draft version and was confident that this article will be of benefit to GPs and medical professionals.

A patient with pernicious anaemia reviewed our manuscript for *The BMJ*. Her diagnosis was similarly delayed. She highlighted the challenges faced by patients in reporting their symptoms during a short GP consultation, and for doctors to connect the dots to make a diagnosis of pernicious anaemia. She suggested that doctors encourage patients or carers to make a list of symptoms. She also suggested discussing the variable course of recovery and about different treatment formulations. We have now covered these points in our article.

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