The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

EASi™
European Autoimmunity
Standardisation Initiative


ThermoFisher
SCIENTIFIC

The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

Pabst Science Publishers
Lengerich, Berlin, Bremen, Miami,
Riga, Viernheim, Wien, Zagreb

Bibliographic information published by Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at <http://dnb.ddb.de>.

http://www.pabst-publishers.de

Printing: MercedesDruck, Berlin
Typesetting: Hilmar Schlegel, Berlin
Cover: Agentur für zeitgemäße Kommunikation Kaner Thompson
www.kanerthompson.de

ISBN 978-3-89967-770-6

Pernicious anemia

Helena Silva, Marilda Santos, João Pedro Ramos, Carlos Dias

1 Introduction

Pernicious anemia (PA) is a form of megaloblastic anaemia secondary to poor cobalamin (Cbl) absorption associated with severe lack of intrinsic factor (IF) due to gastric atrophy. Pernicious anaemia was first introduced by Thomas Addison in 1849, who described it as "a very remarkable form of anaemia" later called pernicious (fatal) by Anton Biermer. PA is an autoimmune disease based on the presence of the autoantibodies anti-gastric parietal cells or anti-IF, supported by the presence of mononuclear cell infiltration into gastric mucosa with loss of parietal cells and by the regeneration of these cells under immune suppression with corticosteroids. In 1934, George Hoyt Whipple, George Richards Minot and William Parry Murphy shared the Nobel Prize in Physiology or Medicine for their work on finding a cure for PA, by including liver in the patient's diet. The active ingredient in the liver extracts remained unknown until 1948, when Cobalamin (Cbl) ("the extrinsic factor") was isolated by two chemists, Karl A. Folkers and Alexander R. Todd. With that discovery, it became possible to treat PA, in a cheap and effective way, by injecting Cbl into muscle. In nature, Cbl exists in 3 major chemical forms in different food resources: methylcobalamin (MeCbl), deoxyadenosylcobalamin (AdoCbl) and hydroxycobalamin. Once metabolised, Cbl is a cofactor and coenzyme in many biochemical processes, including DNA synthesis. As MeCbl, it acts as a cofactor for methionine synthesis from homocysteine. As AdoCbl, it contributes to propionyl conversion into succinyl coenzyme A from methylmalonate. The deficient purine and aminoacid synthesis is responsible for the observed megaloblastic anaemia and other haematological, neurological and multi-organ manifestations.

2 Clinical manifestations

Clinical manifestations are highly polymorphic and range in severity from milder conditions to severe. In asymptomatic patients, PA can be detected on routine blood analysis as a raised mean corpuscular volume (MCV). Symptoms such as

anorexia, fatigue and other symptoms related to anaemia are very common. The most frequent manifestations are sensory neuropathy with isolated macrocytosis, in milder Cbl deficiencies. Haemolytic anemia, pancytopenia and sclerosis of the cord are rare manifestations presenting in severe forms of PA. The classic manifestations related to PA are Hunter's glossitis (lingual papillae atrophy) and the neuroanaemic syndrome (combined sclerosis of the spinal cord and megaloblastic anaemia) (Table 1).

Table 1. Major clinical manifestations related to cobalamin deficiency and present in pernicious anaemia. Adapted from [1].

Clinical manifestations		Frequency
Haematologic	Megaloblastic anemia, macrocytosis, hypersegmentation of neutrophils, medullary megaloblastosis	Frequent
	Isolated thrombocytopenia and neutropenia; pancytopenia	Rare
	Haemolytic anaemia, thrombotic microangiopathy	Very rare
Neuropsychiatric	Degeneration of the spinal cord	Classic
	Peripheral neuropathy, ataxia, Babinsky's phenomenon	Frequent
	Cerebellar syndromes involving cranial nerves, including optic neuritis, optic atrophy, urinary or faecal incontinence	Rare
	Dementia, Parkinsonian syndromes, depression	Under study
Digestive tract	Glossitis, angular queilosis, jaundice, lactate dehydrogenase and bilirubin elevation	Classic
	Diarrhoea, constipation, dyspepsia, abdominal pain	Debatable
	Type A chronic gastritis, atrophic gastritis or gastric atrophy	All patients
	Intestinal metaplasia, gastric neoplasmas: adenocarcinoma, lymphoma, carcinoid tumour; resistant and recurring mucocutaneous ulcers	Rare
Cutaneous	Reversible melanin skin hyperpigmentation	Frequent/Debatable
Cardiovascular	Thromboembolic disease: angina, stroke (hyperhomocysteinaemia)	Under study
Gynaecological	Vaginal mucosa atrophy, chronic vaginal and urinary infections, hypofertility and repeated miscarriages	Under study

3 Diagnostic criteria

There are no definitive diagnostic criteria for PA. However, this disease is diagnosed by clinical manifestations, macrocytic anaemia (MCV >100 fL) (Fig. 1) deficiency of vitamin B 12, confirmed Cbl malabsorption with a positive Schilling test, demonstration of an autoimmune process by specific antibody identification (anti-gastric parietal cells and anti-IF) and type A chronic gastritis, atrophic gastritis or gastric atrophy.

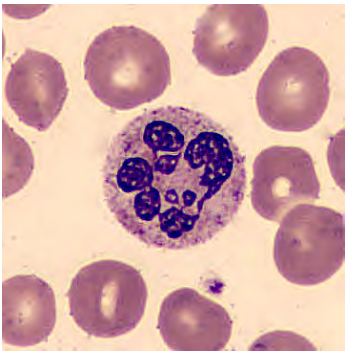

Figure 1. Anisocytosis, macrocytosis and neutrophil hypersegmentation are quite obvious in the blood smear.

4 Diagnostic measurements for experts

Alcohol abuse, oncological background, medication history and patient diet should be well evaluated. Several medical conditions are associated with macrocytic anaemia, with or without detectable vitamin deficiency, and should be suspected after a careful clinical history is obtained. Folate deficiency should also be ruled out. If nutritional deficiencies are excluded or their presence is doubtful, primary bone marrow disease must be carefully evaluated.

5 Requirements for family practitioners

It is important to acknowledge that Cbl deficiency is very prevalent in the general population and occurs frequently among elderly. The same is true for PA and for polyneuropathy (PN), as the frequency of both disorders increases with age. Considering that PA is secondary to parietal cell destruction by autoimmune mechanisms, the consequence is failure to produce IF and a state of achlorhydria (and secondary hypergastrinaemia). Since gastric acid production is very important in food iron absorption, iron deficiency is also a very common complication in PA

and may result in different presentations of anaemia: macrocytic, normocytic or microcytic anaemia. These findings lead to an obvious discussion about iron and Cbl deficiencies overlap, about atrophic gastritis and PA as different entities or different stages in the spectrum of the same autoimmune disease, sharing the same antibodies.

For family practitioners, the challenges are different considering the different settings as PA can be presented.

Pernicious anaemia presenting as isolated macrocytosis: these are asymptomatic patients that, on routine haematologic evaluation, present an elevated MCV without anaemia. Commonly this finding may represent a milder form of vitamin B 12 deficiency with normal values of serum Cbl. The determination of plasma levels of Cbl metabolites (pHC and MMA), if available, may be important for identifying Cbl deficiency probably secondary to PA.

Pernicious anaemia presenting as megaloblastic anaemia: pernicious anaemia is the most common cause of megaloblastic anaemia in Western countries and its diagnosis poses relatively few diagnostic problems in this setting. In this condition, macrocytic anaemia is associated with hypersegmented neutrophils and abnormal nuclei maturation can be detected on several organs. Megaloblastosis is a generalised process where bone marrow, gastrointestinal and gynaecological

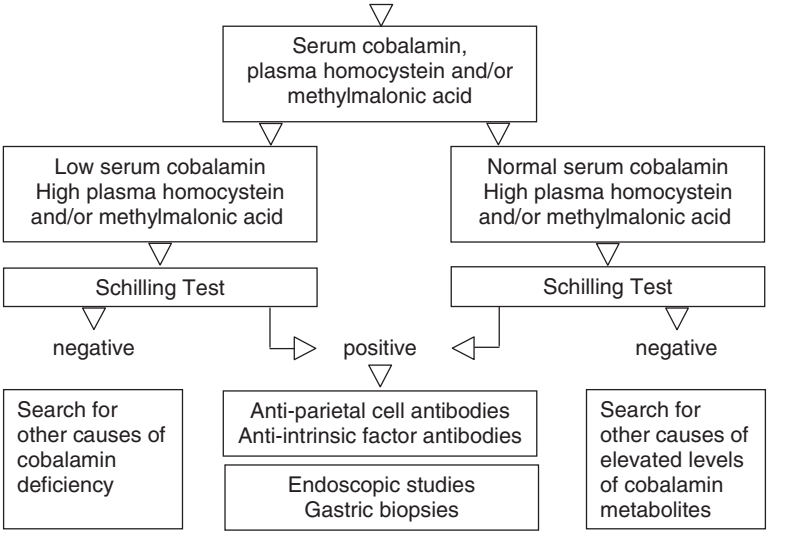

Figure 2. Diagnostic approach for pernicious anaemia.

smears or biopsies present characteristic abnormalities consequent to nuclei delayed maturation.

Pernicious anaemia presenting as polyneuropathy: as both diseases are very frequent in the general population and more frequently among elderly, it is difficult to establish an aetiologic correlation between both disorders, since the cobalamin deficiency has not been proved as the cause of the neuropathy, even in the absence of other causes. Polyneuropathy in Cbl deficiency frequently presents as sensory or sensorimotor polyneuropathy, usually involving upper and lower extremities concomitantly. It usually has a sudden onset and a shorter illness duration and is less likely to present as pain or lower limb weakness compared to cryptogenic polyneuropathy. Patients commonly experience symptom onset in the hands or in the hands and feet simultaneously, traducing small and/or large-fibre sensory involvement. Patients presenting PN associated with cobalamin deficiency have a low incidence of haematologic abnormalities. They are more likely to have erythrocytes with elevated mean corpuscular volumes, but the incidence of anaemia is the same as in cryptogenic neuropathy.

In patients with PN, with or without haematologic abnormalities, it is mandatory to investigate cobalamin deficiency, perform electrodiagnostic studies (such as electromyography, nerve biopsy or lumbar puncture) and expert evaluation (Internal Medicine or Neurology) to investigate other causes.

6 Follow up

Once diagnosis is well established, the follow up procedure will be mainly the clinical monitoring of laboratory abnormalities (serum Cbl) after due treatment. Chronic gastritis (CG) can be classified in clinical stages based on histological findings. Initial stages may present a superficial gastritis with inflammatory changes limited to *lamina propria* on the surface mucosa. In the second stage, designated as atrophic gastritis, inflammation extends deeply into the mucosa with progressive destruction of glandular structures, and progresses to severe gland destruction, gastric atrophy and intestinal metaplasia that ultimately can lead to gastric tumour. It is important to perform regular endoscopic studies (every 3 to 5 years) and, if no lesion is macroscopically identified, several random gastric biopsies must be done.

7 Management

The standard treatment aims to correct body stores and to maintain daily needs. Most patients are treated with intramuscular vitamin B 12, which is time consuming, can be painful, can be inconvenient for anticoagulated patients and, rarely, presents toxic reactions. Effective oral treatment is available in clinical practice,

presenting equal efficacy, similar costs, safety and adherence compared to parenteral administration. The efficacy of oral treatment in PA patients depends on both mechanisms of vitamin B 12 absorption, mainly passive absorption (without IF), but also active absorption of free-vitamin B 12 (associated with IF). In most countries, doctors do not prescribe oral formulations because they are either unaware of this option or have concerns about efficacy due to unpredictable absorption. In the literature, there is limited evidence from randomised control trials (RCTs) that oral vitamin B 12 is an effective treatment for cobalamin deficiency in the short term and no evidence for its efficacy for long term treatments in PA patients. High doses of oral vitamin B 12 (1000 to 2000 μg) initially daily, then weekly and then monthly are as effective as intramuscular administration in achieving haematological and neurological responses (Table 2).

Table 2. Replacement therapy for pernicious anaemia.

Replacement of body stores	Six intramuscular 1000 μg injections of hydroxycobalamin given at 3 to 7 day intervals or
	Daily oral doses (1000 to 2000 μg) of cyanocobalamin
Maintenance treatment	1000 μg of intramuscular hydroxycobalamin every three months
	1000 μg of intramuscular cyanocobalamin monthly (because of poorer retention)
	Daily oral doses (1000 to 2000 μg) of cyanocobalamin

Treatment efficacy is synonymous with reversal of the haematological and neurological manifestations and correction of body stores that should be assessed routinely.

Considering that iron deficiency frequently overlaps Cbl deficiency, oral iron supplementation should be given. Folate deficiency should also be corrected if detected.

8 Diagnostic tests

The first diagnostic approach aims to identify cobalamin deficiency, by the determination of serum cobalamin, which is the screening test. The presence of elevated levels of plasma homocystein (pHC) and methylmalonic acid (MMA) can support the diagnosis and are more sensitive indicators of cobalamin deficiency than cobalamin serum levels alone, especially for the diagnosis of milder forms of vitamin B 12 deficiency. Normal values of pHC and MMA can rule out cobalamin deficiency. It is important to acknowledge that hyperhomocysteinaemia is present in folate and pyridoxine deficiencies (or improper collection and processing of blood samples), and that both pHC and MMA levels are raised in conditions such as renal insufficiency, volume contraction and various enzyme polymorphisms.

The diagnosis of ileum malabsorption requires a Schilling test. This test will confirm vitamin B 12 malabsorption by determining urinary radioactivity after an oral dose of radioactive Cbl is given. Urinary radioactivity is lower when radioactive Cbl is administered along with IF, confirming IF deficiency (or abnormality). After confirming Cbl malabsorption related to IF deficiency, it is necessary to identify antibodies related to the pathological process that defines PA. Sixty to ninety percent of PA patients present with antibodies to gastric parietal cells, but those are also very prevalent in simple atrophic gastritis (60 %) and thyroid disease. Antibodies to IF are less sensitive (found in 50 to 70 % of PA patients) but more specific for PA.

Finally, the evidence of organ disease associated with autoantibodies requires confirming the presence of type A chronic atrophic gastritis or gastric atrophy by endoscopic procedures and gastric biopsy.

References

[1] Andrès E, Loukili NH, Noel E, et al. Vitamin B12 (cobalamin) deficiency in elderly patients. CMAJ 2004; 171: 251–9.
[2] Saperstein DS, Wolf GI, Gronseth GS, et al. Challenges in the identification of cobalamin-deficiency polyneuropathy. Arch Neurol 2003; 60: 1296–301.
[3] Hershko C, Ronson A, Souroujon M, et al. Variable hematologic presentation of autoimmune gastritis: age-related progression from iron deficiency to cobalamin depletion. Blood 2006; 107: 1673–9.
[4] Butler CC, Vidal-Alaball J, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. Fam Pract 2006; 23: 279–85.
[5] Carmel R, Green R, Rosenblatt DS, Watkins D. Update on Cobalamin, Folate, and Homocysteine. Hematology Am Soc Hematol Educ Program 2003: 62–81.