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CLINICAL UP-DATE

Pernicious anemia. From past to present☆

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Abstract Pernicious anemia is currently the most common cause of vitamin B12 deficiency in Western countries. The histological lesion upon which this condition is based is autoimmune chronic atrophic gastritis. The destruction of parietal cells causes a deficiency in intrinsic factor, an essential protein for vitamin B12 absorption in the terminal ileum. Advances in the last two decades have reopened the debate on a disease that seemed to have been forgotten due to its apparent simplicity. The new role of *Helicobacter pylori*, the value of parietal cell antibodies and intrinsic factor antibodies, the true usefulness of serum vitamin B12 levels, the risk of adenocarcinoma and gastric carcinoids and oral vitamin B12 treatment are just some of the current issues analyzed in depth in this review.

PALABRAS CLAVE
Anemia perniciosa;
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Anticuerpos anticélula parietal;

Anemia perniciosa. Del pasado al presente

Resumen Actualmente, la anemia perniciosa es la causa más frecuente de déficit de vitamina B12 en los países occidentales. La lesión histológica sobre la que se sustenta es la gastritis crónica atrófica autoinmune. La destrucción de las células parietales provoca un déficit de factor intrínseco, proteína fundamental para que la vitamina B12 se absorba en el íleon terminal. Los avances que se han producido en las dos últimas décadas han reabierto el debate sobre una enfermedad que parecía olvidada por su aparente simplicidad. El nuevo papel del H. pylori,

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Anticuerpos antifactor intrínseco;
Homocisteína;
Ácido metilmalónico;
Riesgo adenocarcinoma gástrico;
B12 oral

el valor de los anticuerpos anticélula parietal y antifactor intrínseco, la verdadera utilidad de los niveles séricos de vitamina B12, el riesgo de adenocarcinoma y carcinoides gástricos o el tratamiento con vitamina B12 oral, son algunos de los temas de actualidad que se analizan en profundidad en esta revisión.

Case report

A 29-year-old man with a history of asthma and allergic rhinoconjunctivitis visited our office for symptoms that had progressed for 2 months. The symptoms were asthenia, nonspecific dizziness and intermittent, moderately intense epigastric pain. The examination revealed pronounced pallor of the skin and mucous membranes. The laboratory tests indicated a hemoglobin level of 6 g/dL (13–18 g/dL), mean corpuscular volume of 120 fl (80–100 fl), leukocyte count of 5400 mL^{-1} (4000–10,500 mL^{-1}), platelet count of 275,000 mm^{-3} (150,000–400,000 mm^{-3}), total bilirubin of 1.29 mg/dL (0.3–1.2 mg/dL), indirect bilirubin of 0.79 mg/dL, aspartate aminotransferase (AST) level of 135 IU/L (4–50 IU/L), alanine aminotransferase (ALT) level of 401 IU/L (5–47 IU/L) and lactate dehydrogenase (LDH) level of 4256 IU/L (140–240 IU/L). Given these findings, a blood smear was requested, which revealed anisocytosis with a tendency toward macrocytosis, neutrophil hypersegmentation and some dacrocytes. Iron and folic acid levels were normal, with a serum vitamin B12 level of 57 pg/mL (180–880 pg/mL) and homocysteine level of 24 μmol/L (4–15 μmol/L). Gastrin levels were clearly high at 551 pg/mL (normal <100 pg/mL). How should the diagnosis and therapy for this patient be approached?

Background

The 22nd edition of the Royal Academy of the Spanish Language provides the following definition for the adjective ''pernicious'': from the Latin *perniciōsus*, that which is seriously harmful or disruptive. The history of this disease began in 1855, when the US physician Thomas Addison described a case of a patient with pallor, sickly appearance, generalized weakness and progressive intolerance to effort.[1] During the second half of the 19th century, the adjective pernicious became popular among the scientific community for characterizing patients who had this devastating disease, also known as Biermer's disease. Thanks to figures such as the dedicated William Castle and his characterization of the intrinsic factor, to Whipple and Murphy (winners of the Nobel Minot prize) for discovering that the dietary intake of raw liver drastically improved survival and to groups at the University of Cambridge and Harvard for their work on vitamin B12, a Copernican turn has occurred in the outcome of patients with this condition, which in the past resulted in the unstoppable death of the patient.

Today's clinicians tend to trivialize and simplify the diagnosis and management with a ''You have a low vitamin level. Take 1 injection a month and don't worry.'' However, there are numerous points of contention and uncertainty that warrant a review and reflection on the topic: What exactly is the etiology? Has the diagnostic process proceeded correctly? What does a low serum vitamin B12 level really mean? Is follow-up appropriate? Is there a real risk of gastric adenocarcinoma and carcinoid? Vitamin B12; how much and how often?

Epidemiology

Pernicious anemia has traditionally been considered a disease that affects women older than 60 years who were born in northern Europe. However, extensive case series published in the last 30 years have confirmed that pernicious anemia can present in individuals of any race, sex, age and continent.[2–4]

Although it is clear that the condition is more common in elderly patients, up to 50% of cases occur in those younger than 60 years.[5] In contrast to that postulated in the second half of the 20th century, there is no clear difference in its frequency between sexes.[5] The patient presented above is a clear example of this new epidemiological reality.

There are no current epidemiological studies that provide specific figures on the situation in Spain; however, it is estimated that its prevalence in European countries is approximately 4% of the population.[6] Given that the condition progresses silently or paucisymptomatically for much of its natural history, its incidence and prevalence are underestimated.

What causes it?

In large part, the causes are applicable to general human pathology: on a partially known genetic basis, a number of exogenous and environmental factors are involved, which are not completely understood and that can trigger an autoimmune pathophysiological process.

There are two key facts that confirm a *genetic basis*. First, pernicious anemia has familial clustering; up to 19% of patients have a family member who is affected.[7] Second, its association with 2 haplotypes of the major histocompatibility complex type II has recently been reported: HLA-DRB1*03 and HLA-DRB*04.[5]

In terms of the *exogenous factors*, the role of *Helicobacter pylori* deserves special attention. Historically, gastritis