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Pernicious anaemia in triplets. A case report an literature review

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ABSTRACT

Pernicious anemia is the most common cause of vitamin B_{12} deficiency in adults. This entity is associated with chronic atrophic gastritis. We report a case of pernicious anaemia in triplets. We also report a fourth case of cobalamin deficiency with antibodies against intrinsic factor and antiparietal cell antigen negative antibodies in a sibling. The present article reviews the pediatric presentation of pernicious anemia and highlights the possible existence of familial aggregation. Furthermore, the need for systematic familial screening and the usefulness of an endoscopic follow-up program in patients with pernicious anemia are evaluated.

ANEMIA PERNICIOSA EN TRILLIZOS. CASO CLÍNICO Y REVISIÓN DE LA LITERATURA MÉDICA

La anemia perniciosa es la causa más frecuente de déficit de vitamina B_{12} en adultos. Esta entidad se ha asociado con la gastritis crónica atrófica. En este trabajo se describe la existencia de anemia perniciosa en 3 hermanas trillizas. Asimismo, también se describe un cuarto caso de déficit de cobalamina con anticuerpos antifactor intrínseco y negatividad para anticuerpos anticélula parietal gástrica en una hermana no trilliza. En este trabajo se revisa la presentación pediátrica de la anemia perniciosa, así como la posible existencia de una agregación familiar. Por otra parte, se ha evaluado la necesidad de realizar un estudio sistemático de los familiares y el beneficio de establecer un protocolo de seguimiento endoscópico de los pacientes con anemia perniciosa.

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INTRODUCTION

Pernicious anaemia (PA) is the most common cause of vitamin B_{12} deficiency in adults. PA is associated with type A chronic atrophic gastritis, autoantibodies to gastric parietal cells and to intrinsic factor, achlorhydria, low serum pepsinogen concentrations and high serum gastrin levels. Histological changes (chronic atrophic gastritis) may be detected years before the anaemia is manifested, and the progression of chronic atrophic gastritis to clinical anaemia is likely to 20-30 years[1]. PA usually remains silent until end-stage, and some studies consider that up to 2 percent of the general population older than 60 years-old have undiagnosticated PA[1]. However, macrocytic anaemia is not the only haematological presentation of atrophic gastritis. In 27% of patients with iron deficiency anaemia, atrophic gastritis is present[2]. In developed countries, cobalamin deficiency in children and young adults is more often secondary to ileal diseases, and diagnosis of PA is rare.

Some authors have described a familial disease aggregation in PA, but systematic familial screening has not been recommended as a rule. We report a case of familial PA in 3 young adult triplets.

CASE REPORT

A 27-year-old woman with a history of psoriasis complicated with psoriatic arthritis was referred to our hospital for the study of a normocytic anaemia. At that moment, physical examination was normal, and blood analysis revealed haemoglobin 9.7 g/dl, hematocrit 29.8%, MCV 73 fL, platelet count 261 $\times$ 10^9/l, normal serum ferritine and folate, and a vitamin B_{12} deficiency of 102 pg/ml (normal range, 250-850). The remaining hematologic parameters, hepatic biology, and renal function were within the normal range. Antibodies against parietal-cell antigen (aPCA) were strongly positive (1/1280), although antibodies against intrinsic factor (aIFA) were negative. Screening serology for celiac disease (atTG, antiendomisial) was also negative. Seric gastrinemia was highly increased (1166 pg/ml, normal range 0-90), and seric pepsinogen levels were decreased (19.1 ng/ml, normal range 34-169). Endoscopic gastric biopsies showed chronic gastritis without inflammatory infiltrate but with a marked focal reduction in the number of gastric glands, and without *Helicobacter pylori* infection. A screening study of pernicious anemia was carried out in two monozygotic triplets of the patient. In one of them, a mild normocytic anemia was found, with seric ferritin of 1 ng/ml, vitamin B_{12} of 126 g/ml, positive aPCA 1/169, with negative

aIFA, but positive atTG. Increased gastrinemia and low seric pepsinogen were also found. The gastric biopsy demonstrated a chronic atrophic gastritis, and duodenal biopsy ruled out celiac disease. In the remaining triplet, a mild normocytic anemia with vitamin B_{12} deficiency, positive aPCA, increased gastrinemia and low seric pepsinogen levels, was also shown. Gastric biopsies were diagnostic of chronic atrophic gastritis.

After PA diagnosis in all three triplets, an older sister was likewise evaluated. Although a mild normocytic anemia with low seric cobalamin levels was observed, negative aPCA and aIFA, normal seric concentration of gastrin and pepsinogen, and normal gastric histology ruled out PA. Ileal disease was ruled out by means of ileocolonoscopy and ileal biopsies, as well as an intestinal barium-meal follow-through. Fecal elastase show a normal exocrine pancreatic function. Cobalamin levels returned to normal range after parenteral administration for a few months, and remained stable thereafter.

DISCUSSION

Although several clinical settings may course with cobalamin deficiency (such as pancreatic insufficiency, malabsorption syndromes –including tropical sprue and celiac disease–, gastrectomy, ileal resection, bacterial overgrowth, and specific genetic disorders)[3], PA is considered the most common cause of vitamin B_{12} deficiency, especially, in elderly patients.

There are two main mechanisms responsible of cobalamin malabsorption in PA. First, there is a progressive loss of parietal cells from the gastric mucosa that lead to the failure of intrinsic factor production. Second, the autoantibodies present in the gastric juice can bind to the vitamin B_{12}-binding site of intrinsic factor, and block the formation of the vitamin B_{12}-intrinsic factor complex. The damage of parietal cells also abolishes acid secretion, that leads to achlorhydria. Likewise, gastric acid secretion, is necessary for the solubilization and reduction of food iron permitting normal iron absorption. In turn, iron deficiency is a known complication of pernicious anemia at disease presentation or following cobalamin treatment[4]. In PA patients, the co-existence of iron deficiency can occur in up to 20% of patients at initial diagnosis and in another 20% of patients during a 2-year follow-up[2,5]. In contrast to the adult onset of the disease, childhood PA, is not associated with achlorhydria or chronic atrophic gastritis. Some authors suggested that this pediatric presentation of PA might be the result of a genetically determined failure to secrete intrinsic factor or even the secretion of a defective intrinsic factor[6].

A genetic predisposition to PA has been suggested[7,8]. In fact, several authors have reported familial aggregability of PA[6], and up to 20 percent of the relatives (mainly first-degree female relatives) of PA patients are also affected[1,9,10]. Furthermore, a cluster of PA and gastric autoantibodies with autoimmune endocrinopaties has been also reported[4]. However in recent reviews, *Helicobacter pylori* has been involved in the development of atrophic gastritis, and it is well established that *H. pylori* infection can induce gastric autoimmunity. In addition, two-thirds of patients with atrophic gastritis and a large proportion of PA patients, have co-existing *H. pylori* infection[11]. By now, familial screening is not advised among new-diagnosed PA relatives.

Patients with PA are at a greater risk for the development of gastric neoplasms (both carcinoid and adenocarcinoma). This population have a prevalence of 1-3% and a risk three times more than the general population for development of gastric carcinoma[12]. Intestinal metaplasia and atrophic gastritis associated with achlorhydria have been postulated as potencial pathogenic factors for the development of gastric cancer in patients with PA. Although they have to be considered as a high risk group, guidelines for cancer screening in these patients are still lacking. In clinical practice, gastroscopy is performed periodically in most of PA patients. There is no agreement in the appropiateness of routine endoscopic screening in patients with PA[12-15]. In these sense, a recent retrospective study found a low incidence of gastric cancers or dysplasia in a series of 68 PA patients followed-up with biannual endoscopies[16]. The authors suggested that a biannual endoscopic follow-up is not necessary and that, gastroscopic surveillance must be performed in longer periodicity. More studies are needed to define the best endoscopic follow-up (in terms of periodicity and/or subgroups of patients) for the early detection of gastric neoplasms in patients with PA.

The present case-report underlines the existence of familiar aggregation (and, in turn, genetic factors) in PA. Two out of the three patients were diagnosed while being clinically asymptomatic, although they had a significant cobalamin deficiency. Taking into account that PA is a known risk factor for gastric neoplasms, familial screening might be of relevance in case of twins, but systematic familial screening in all PA patients has to be accurately evaluated in the setting of prospective studies.

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