Carol Rees Parrish, MS, RDN, Series Editor

# Chronic Atrophic Gastritis: Don't Miss These Nutritional Deficiencies

Craig R. Gluckman

**Chronic atrophic gastritis (CAG) results in the destruction of gastric mucosa parietal cells leading to reduced gastric acid secretion and decreased intrinsic factor (IF) production. The consequence of which is achlorhydria, hypergastrinemia, and IF deficiency. As a result, CAG may lead to the malabsorption (albeit by different mechanisms) of vitamin B12 and iron, causing macrocytic anemia or iron deficiency anemia, respectively. Vitamin B12 deficiency, due to decreased IF production can result in megaloblastic anemia and varying neurologic dysfunction. The mechanism of iron deficiency in CAG is less clear but felt likely due to achlorhydria or concomitant Helicobacter pylori infection. In addition, other vitamin and micronutrient deficiencies (such as vitamin D, calcium and vitamin C) have been known to occur in patients with CAG, although the mechanisms for these have been less well studied. This article will review the nutritional deficiencies as a consequence of CAG.**

## INTRODUCTION

Chronic atrophic gastritis (CAG) results in atrophy of the gastric body mucosa and the chronic loss of gastric parietal cells. These parietal cells, under the influence of gastrin (from G cells) and histamine (from ECL cells), stimulate acid production and lead to decreased pH in the gastric lumen.[1] The parietal cells also control intrinsic factor (IF) production by a different mechanism. This parietal cell loss leads to reduced gastric acid secretion and decreased IF production. The cause of atrophic gastritis (AG) is either (i) the immune-mediated destruction by antibodies (IF and/ or parietal cell) directed against the gastric mucosa (termed chronic atrophic autoimmune gastritis (CAAG)) or (ii) Helicobacter pylori (H. pylori) infection. Regardless of the cause, the net effect of parietal cell loss and gastric atrophy is achlorhydria, which induces G cell hyperplasia and the secretion of additional gastrin resulting in hypergastrinemia.[2] Significantly, each of the above-mentioned causes of CAG harbor an increased risk for gastric neoplasia, including gastric adenocarcinoma and Type 1 gastric carcinoids, particularly when extensive gastric intestinal metaplasia is present.[3] Therefore, in populations at low risk for gastric cancer (like in the U.S.), endoscopic surveillance every 3 years should be offered to patients with extensive atrophic gastritis or intestinal metaplasia.[4]

CAG leads to the malabsorption of food-bound vitamin B12 due to decreased IF production resulting in megaloblastic anemia (a type of macrocytic anemia) and demyelinating neurologic

Craig R. Gluckman, MD Clinical Instructor of Medicine, Division of Digestive Disease, UCLA Health, West Hills, CA

disease. A deficiency of folate can result in a similar clinical picture. The terms 'megaloblastic anemia' and 'macrocytic anemia' should not be used interchangeably, as not all causes of macrocytosis are due to vitamin B12 deficiency but all causes of megaloblastic anemia are due to B12 (or folate) deficiency. In contrast, the mechanism for iron deficiency anemia (IDA) in atrophic gastritis is less clearly understood, but likely due to achlorhydria or H. pylori-associated atrophic gastritis. It is therefore vital to exclude atrophic gastritis caused by H. pylori infection in any patient presenting with an unexplained IDA, as this is treatable.

CAAG may occur as part of the polyglandular autoimmune syndrome and may be associated with other autoimmune diseases such as type I diabetes, vitiligo, and thyroid disease; therefore, these associated conditions should be considered during the evaluation of CAG. In addition, other vitamin and micronutrient deficiencies (including vitamin D, calcium and vitamin C) have been known to occur in patients with CAG, although their frequency and likely mechanism of onset is less well understood.

The endoscopic appearance of CAG may not be different from normal mucosa, especially during the early disease state.[5] Therefore, if CAG is clinically suspected, the endoscopist at the time of upper endoscopy should perform biopsies according to the updated Sydney protocol (two from the corpus, two from the antrum, and one from the angularis),[6] as well as targeted biopsies of any visible lesions. It should be noted there may be endoscopic findings other than gastric body mucosal atrophy such as gastric polyps or Type I gastric neuroendocrine tumors (Image 1).

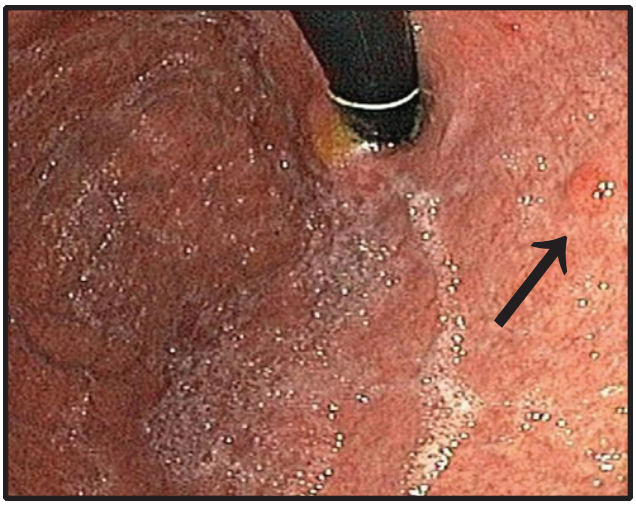

**Image 1. Gastric Atrophy with Gastric Carcinoid (Arrow)**

## Vitamin and Micronutrient Deficiencies

### *Vitamin B12 Deficiency*

The absorption of food-bound vitamin B12 is mostly dependent on the glycoprotein IF which is produced by gastric parietal cells. The vitamin B12-IF complex is ultimately absorbed in the terminal ileum. In CAG, there is a lack of IF production due to parietal cell destruction causing downstream reduced vitamin B12 absorption. Megaloblastic anemia due to vitamin B12 (or folate) deficiency leads to defective production of erythrocytes and DNA synthesis, hence the macrocytic red blood cells. In CAAG, the presence of autoantibodies directed against IF and/or parietal cells results in pernicious anemia (PA). Testing for both antibodies significantly increases their diagnostic performance for diagnosing CAAG and PA, yielding a 73% sensitivity and 100% specificity for PA.[7] The immune destruction of parietal cells leads to decreased IF production which results in PA, especially common in Westernized countries and the elderly. The other conditions causing vitamin B12 deficient megaloblastic anemia (Table 1) need to be differentiated from CAAG which causes PA from IF deficiency.

A lack of vitamin B12 affects the two human enzymes that require it, namely methionine synthase (cytoplasm) and methylmalonyl-CoA mutase (mitochondria) and gives rise to elevated levels of homocysteine and methylmalonic acid (MMA), respectively.[8] In borderline cases of vitamin B12 deficiency, the elevation of homocysteine and MMA can confirm the diagnosis, especially when other compatible clinical or biochemical findings are present. Interpret homocysteine and MMA levels with caution in renal failure and pregnancy where falsely elevated levels may occur. Elevated plasma homocysteine is now recognized as an independent risk factor for cardiovascular disease and seems to play an important role in the development of dementia, diabetes mellitus and renal disease.[9] Homocysteine is also elevated in folate deficiency.

The clinical sequela of vitamin B12 deficiency

(Table 2) range from asymptomatic to varying degrees of hematological and neurological dysfunction, which may or may not be reversible with supplementation. The classic neurological presentation of a patient with PA is proprioceptive sensory loss with ataxic gait abnormalities, demyelinating peripheral sensory-motor polyneuropathies and paresthesias. Cognitive changes may also be seen including amnesia, apathy, depression and ultimately more serious cognitive decline. In the most severe forms of vitamin B12 deficiency, there may be complete myelopathy with sub-acute degeneration of the spinal cord and blindness due to optic atrophy. The myriad hematological manifestations include megaloblastic anemia (because of impaired DNA synthesis and erythropoiesis) with pancytopenia despite a hypercellular bone marrow.

There appears to be a reduced awareness of CAG and its clinical consequences amongst physicians, often leading to a significant diagnostic delay. This could result in the potential diagnosis of vitamin B12 deficiency being overlooked for many months. A recent study from Italy that looked at 291 patients with CAG found that the median overall diagnostic delay was 14 months (interquartile range [IQR] 4-41), particularly amongst gastroenterologists.[10] Clearly there is a need for increased education and awareness of this condition, and treating physicians need to maintain a high index of suspicion.

Whether acid blocking drugs like proton pump

**Table 1. Cause and Likely Mechanism of Vitamin B12 Deficiency**

| | Cause of Vitamin B12 Deficiency | Likely Mechanism |
|---|---|---|
| **IF Deficiency** | Atrophic autoimmune gastritis (pernicious anemia) | Antibodies to IF and/ or parietal cells |
| | Post gastrectomy or gastric bypass surgery | Loss of parietal cell mass |
| | Other gastritidies (caustic, H. pylori) | Parietal cell damage or atrophy |
| **Vitamin B12 Malabsorption in the Terminal Ileum** | Ileal resection, tropical sprue or Crohn's disease | Absent site of absorption |
| | Imerslund-Gräsbeck syndrome | Mutations of ileal receptor |
| | Metformin, acid reducing drugs | Unclear |
| **Dietary Deficiency** | Vegan or vegetarian diet | Vitamin B12 deficient food |
| | Breast-fed infants | Vitamin B12 deficient mothers |
| **Other** | Nitrous oxide exposure | Inactivates methionine synthase |

**Table 2. Clinical Findings in Vitamin B12 Deficiency**

| | |
|---|---|
| **Neurological** | **Central Nervous System**<br>Cognitive decline, amnesia, apathy, depression, "megaloblastic madness", optic atrophy |
| | **Peripheral Nervous System**<br>Sensory-motor neuropathy, proprioceptive loss, paresthesia, gait ataxia, myelopathy, sub-acute combined degeneration of the spinal cord |
| **Hematological** | **Bone Marrow**<br>Hypercellular bone marrow, increased erythroid precursors, ineffective erythropoiesis |
| | **Peripheral Blood**<br>Macrocytic anemia (MCV > 90 fL), hyper-segmented PMNs, thrombocytopenia, pancytopenia, hemolysis, elevated methylmalonic acid and homocysteine |
| **General** | Pallor, lethargy, edema, jaundice, glossitis, anorexia, infertility |

inhibitors (PPIs) and $H_2$- receptor antagonists can lead to a clinically significant vitamin B12 deficient state remains up for debate. It is unclear if the effects of these drugs on serum vitamin B12 are associated with increased risk of biochemical or functional deficiency (as indicated by elevated blood concentrations of homocysteine and MMA) or clinical deficiency (including megaloblastic anemia and neurologic disorders).[11] A recent expert review and best practice advice statement from the American Gastroenterological Association recommended that long-term PPI users should not routinely raise their intake of vitamin B12 beyond the recommended daily allowance, nor should they routinely screen or monitor vitamin B12 levels.[12]

The route of replacement of vitamin B12 in a deficient patient has also become somewhat of a controversial issue. Most patients with clinical vitamin B12 deficiency have malabsorption and require either intramuscular (IM) or high-dose oral replacement. Those with CAAG causing PA will need lifelong supplementation. A recent Cochrane review by Wang et al. showed that oral and IM vitamin B12 supplementation have similar effects in terms of normalizing serum vitamin B12 levels, but oral treatment costs less.[13] However, the quality of evidence was low given the shortage of high-quality comparative studies. Therefore, a suggested supplementation regimen would be vitamin B12 at a dose of 1000 mcg administered IM daily or every other day for 1 week, then weekly for 4 to 8 weeks, and then monthly for life, or oral vitamin B12 at a daily dose of 1000 to 2000 mcg for life.[14]

### Iron Deficiency

In patients with CAG, in addition to vitamin B12 deficiency, there may be a preceding or overlapping iron deficiency anemia (IDA) with age being an important factor as to which presents first. Younger patients are more likely to present with features of IDA whereas those over the age of 60, tend to have megaloblastic vitamin B12 deficiency. The variable age-dependent presentation of anemia in patients with CAG reflects the higher prevalence of active H. pylori infection in younger patients.[15] As a result, red cell indices like mean cell volume (MCV) may be unreliable in patients with CAG, as two separate or overlapping deficiencies may be present (the one raising the MCV and the other one lowering it), hence it appears within normal limits.

The possible role of achlorhydria in the development of iron malabsorption has been suggested in different hypo/ achlorhydria models.[16] Low gastric acid secretion results from parietal cell loss. This low gastric acid production leads to decreased food iron solubilization and decreased iron absorption. Therefore, IDA is a common presentation in CAG, but is often overlooked. In a study of 160 patients diagnosed as having autoimmune gastritis by the combined presence of hypergastrinemia and strongly positive anti-parietal cell antibodies, 83 (52%) presented with IDA manifested by low serum ferritin levels, low transferrin saturations, and microcytic anemia.[17]

The presence of IDA due to H. pylori infection in patients with CAG is more complex. It has been shown that up to two-thirds of atrophic gastritis patients have evidence of H. pylori infection. This high prevalence suggests the infection could have a specific role in the disease and not just a mere association.[18] Therefore, it is essential H. pylori is actively excluded in all patients with CAG (or pernicious anemia), so as not to miss a concomitant IDA. It has also been observed that failure to respond to oral iron treatment was more than twice as common in H. pylori positive patients compared to H. pylori negative patients, suggesting that H. pylori infection alters the response to oral iron treatment in IDA.[19] The cure of H. pylori infection is associated with reversal of iron dependence and recovery from IDA.[20] Therefore, eradication of H. pylori, together with oral iron replacement, is essential in the management of patients with CAG and IDA.

### Vitamin D and Calcium Deficiency

There are limited studies suggesting osteopenia and osteoporosis (due to vitamin D and calcium malabsorption) are more common in conditions associated with hypo/achlorhydria, such as post gastrectomy, chronic PPI users and atrophic gastritis. The precise mechanism leading to this association is unclear and the available evidence is controversial. A recent study from Italy evaluated the prevalence of 25-OH-vitamin D (25(OH) D) deficiency in a cohort of 87 patients with CAG. They found in the CAG group, the mean 25(OH) D levels were significantly lower than in the control group

(18.8 vs. 27.0 ng/ ml, $p < 0.0001$). Additionally, the CAG patients with moderate/severe gastric atrophy had lower 25(OH) D values as compared to those with mild atrophy.[21] This suggests that the severity of gastric atrophy is associated with the degree of 25(OH) D malabsorption.

As indicated above, any condition leading to hypo/achlorhydria can result in calcium malabsorption by unclear mechanisms. Gastric acid plays an important role in calcium absorption as it increases the dissolution and ionization of poorly soluble calcium.[22] Recker et al. found that in patients with achlorhydria, the absorption of calcium carbonate was less than in controls with normal gastric acid.[23] Further studies are clearly needed to evaluate whether vitamin D and calcium malabsorption in CAG patients is clinically significant and warrants monitoring.

It also has been suggested that vitamin B12 deficiency in patients with atrophic gastritis likely plays a role in vitamin D deficiency (and calcium malabsorption). Vitamin B12 deficient patients have less osteoblastic activity and bone formation[24] and greater risk of bone fracture.[25] Of note, both men and women with lower vitamin B12 levels had lower average bone mineral density than controls.[26] More research into the relationship between vitamin B12, vitamin D and calcium deficiency, and their potential association with reduced bone mineral density and increased fracture risk in patients with CAG, is needed.

### *Vitamin C Deficiency*

The likely mechanism of vitamin C deficiency in CAG appears to be different from those described above. Older studies proposed a deficiency of vitamin C due to malabsorption, insufficient intake, increased metabolic requirement and rapid destruction in the GI tract.[27] Elevated pH (from achlorhydria) and bacterial overgrowth may also be a factor.[28] Alt et al. evaluated the effect of pH on ascorbic acid stability in vitro and demonstrated the destruction of 65% of the ascorbic acid at pH 7.95 vs only 14% at pH 1.45.[29] The antioxidant effects of vitamin C may provide protection from gastric atrophy and a reduction in the incidence of gastric cancer.[30] Further studies into the consequences of vitamin C deficiency in gastric diseases are clearly needed.

## CONCLUSION

Atrophic gastritis, regardless of its cause, leads to nutritional deficiencies through parietal cell atrophy and the resulting achlorhydria. Vitamin B12 deficiency is well described, but often diagnosed late. A patient with an unexplained iron deficiency anemia should have atrophic gastritis (and concomitant H. pylori) excluded. The significance of vitamin D, calcium and vitamin C malabsorption in chronic atrophic gastritis remains to be seen. ■

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