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Alimentary Tract

Deficiency of micronutrients in patients affected by chronic atrophic autoimmune gastritis: A single-institution observational study

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ABSTRACT

Background: Chronic atrophic autoimmune gastritis (CAAG) leads to vitamin B_{12} deficiency, but other micronutrient deficiencies are largely understudied.
Aims: To investigate the prevalence of micronutrient deficiencies in CAAG patients and their potential relationship with the grading of gastric atrophy or entero-chromaffin-like cells hyperplasia or body mass index (BMI).
Methods: From 2005 to 2016 a number of CAAG patients underwent regular follow-up with annual blood testing and upper gastrointestinal tract endoscopy every years.
Results: Out of the 122 CAAG patients checked (100 F; median age 65 years), 76 presented nutritional deficiencies, single in 24 and multiple in 52 cases: a deficiency of B_{12} and iron showed in 42 patients, 25-OH vitamin D lacked in 76 and folic acid in 6 cases. 25-OH vitamin D levels directly correlated with B_{12} levels and were significantly lower in patients with macronodular than in those with linear or micronodular hyperplasia. No significant correlation was observed between B_{12}, folic acid or ferritin levels and BMI, blood gastrin levels, the grading of gastric atrophy or ECL cells hyperplasia.
Conclusions: 25-OH vitamin D deficiency was the main one in CAAG patients: its correlation with B_{12} deficiency may indicate underlying shared pathogenic mechanisms, although further studies are needed to confirm this hypothesis.

1. Introduction

Chronic atrophic autoimmune gastritis (CAAG) is an organ-specific autoimmune disease characterized by the presence of auto-antibodies against the proton-pump H+/K+ adenosine triphosphatase, present in the gastric parietal cells, and the intrinsic factor, to a lesser extent [1]. CAAG, which is frequently associated with other autoimmune diseases [2–5], occurs in approximately 2% of the general population, with higher prevalence in females, particularly those older than 60 years [6], although a recent Swedish study has reported a higher incidence between the ages of 35 and 45 years [7]. Old age, female sex, the presence of other autoimmune diseases [8–11] and *Helicobacter pylori* (*H. pylori*) infection are the main risk factors for the development of CAAG [12–14], even if genetic predisposition is supposed to contribute to its pathogenesis [15–17]. CAAG is characterized by the progressive lymphocyte T-mediated destruction of parietal and zymogenic cells, which are replaced by intestinal metaplasia [18,19]. These alterations result in achlorhydria, intrinsic factor deficiency, hypergastrinemia and entero-chromaffin-like (ECL) cells hyperplasia [20].

To date, the vitamin deficiency mostly observed in patients with CAAG is vitamin B_{12} deficiency, due to the reduction of the intrinsic factor levels [21]. However, more recently, iron deficiency and iron-deficiency anemia (IDA) have been also reported in the setting of CAAG, particularly in younger patients [22,23], frequently preceding the onset of B_{12} deficiency [24,25]. Indeed, the gastric secretion of hydrochloric and ascorbic acids is important for the solubilization and reduction of non-heme food iron to normal iron absorption [25–28].

Moreover, the deficiency of other vitamins and micronutrients, such as vitamin C, vitamin D, folic acid and calcium, have been described in patients with CAAG or long-standing achlorhydria due to proton-pump inhibitors (PPIs) therapy or gastrectomy [29,30]. The pathogenic mechanism underlying these changes seems to be

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the increased destruction or decreased absorption of nutrients in the gastric mucosa, possibly because of elevated pH and bacterial overgrowth.

- However, to date there are no studies investigating the possible role of CAAG in the occurrence of micronutrients deficiency. The present study aims at consecutively evaluating the prevalence of the deficiency of micronutrients (vitamin B_{12}, 25-OH vitamin D, folic acid, iron, calcium, magnesium, phosphate) in a cohort of patients with CAAG and the potential relationship of such deficiencies with the grading of gastric atrophy or ECL cells hyperplasia and the body mass index (BMI).

2. Materials and methods

From January 2005 to January 2016, 122 patients (100 females, 22 males, median age: 6 years, range 25–90 years) with previously or newly diagnosed CAAG and followed at our Gastroenterology Unit, were consecutively studied.

The diagnostic criteria included: the presence of anti-parietal cell antibodies (APCA) or anti-intrinsic factor positivity, elevated blood gastrin levels and the presence of histology suggestive of CAAG (intestinal metaplasia or pseudopyloric metaplasia or atrophy of the gastric fundus or body). The criteria for exclusion were: ongoing *H. pylori* infection, renal failure, pancreatic insufficiency, severe hepatic failure, previous (in the year before enrollment) or ongoing vitamin or mineral supplementation, or ongoing gastric antisecretory therapy.

The patients underwent annual gastroenterological visits and blood testing including parathormone (PTH), 25-OH vitD, vitamin B_{12}, ferritin, total and ionized calcium, phosphate, magnesium and gastrin levels. The results of 25-OH vitD were compared with a control group of 1232 outpatients matched for sex and age (276 females, median age 56 years and range 18–86 years) managed by the central laboratory of our hospital: subjects with ongoing vitD supplementation, advanced neoplasia, previously known primary hyperparathyroidism and renal insufficiency were excluded from the control group. The BMI and presence of APCA and other autoimmune diseases were evaluated for all the patients. Moreover, upper gastrointestinal tract endoscopy was performed on all the patients every three years.

All the subjects gave their written informed consent to participate in the study, which was approved by the local Ethics Committee.

2.1. Laboratory investigations

The levels of total and ionized calcium (Ca_2^+), phosphate (P), magnesium, intact PTH, 25-OH vitD, vitamin B_{12}, ferritin and gastrin were measured out of venous blood samples obtained after overnight fasting; anticoagulant-free tubes were used for the serum samples and tubes containing EDTA (1 mg/ml of blood) or heparin were utilized for the plasma ones.

Plasma ionized calcium was measured using a potentiometric method (Radiometer ABL System 625, Copenhagen, Denmark) on heparinized blood samples within 30 min of blood collection (reference range: 1.15–1.29 mM). Serum intact PTH was measured by chemiluminescence (Elecsys Intact PTH assay, F. Hoffmann-La Roche, Basel, Switzerland) with 6.0 pg/ml sensitivity. 25-OH vitD was measured using a chemiluminescent, direct and competitive quantitative method (DiaSorin, Saluggia, Italy) with 4.0 ng/ml sensitivity. Plasma gastrin levels were measured using a commercially available RIA Kit (DiaSorin, Stillwater, MN, USA), with alpha sensitivity of 6 pg/ml (normal range: <108 pg/ml). APCA were detected by indirect immunofluorescence assays (NOVA Lite® Rat Liver, Kidney, Stomach Kit, Inova Diagnostics Inc., San Diego, CA, USA).

2.2. Endoscopic investigation

Upper gastrointestinal tract endoscopy was performed with standard gastroscopes (Pentax EG-2970K Video Gastroscope, Pentax® Medical; Pentax EG-2990i High Definition Video Gastroscope, Pentax® Medical; Pentax EG29-i10 High Definition Video Gastroscope, Pentax® Medical). At least 6 gastric biopsies were available for all the patients: 4 from the gastric body and fundus and 2 from the antrum with additional sampling of all the potential lesions. The biopsies were fixed in Bouin's fluid for 4–5 h at 18 °C and then rinsed in 70 ethanol/30 water, dehydrated and fixed in paraffin.

The grading of gastric atrophy was classified as mild, moderate or severe, according to the Sydney classification [31]. The status of the ECL cells was classified as absent, linear, micronodular or macronodular, according to Solcia et al. [32].

2.3. Statistical analysis

The results are given as median and range. All the data were tested for normal distribution with the Kolmogoroff–Smirnoff test. Differences between groups were evaluated by the Kruskal–Wallis test and Mann–Whitney's test, followed by Dunn's multiple comparisons test whenever necessary. The possible relationships between variables were evaluated with Spearman's correlation coefficient test. A p-value <0.05 was considered statistically significant.

In order to evaluate whether the number of groups was adequate, a *post-hoc* power analysis was performed, assuming an equal effect size in the sample and in the general population. Analyses were performed using GraphPad Prism version 5.00 and GraphPad State Mat version 2 for Windows (GraphPad Software, San Diego, CA, USA).

3. Results

The main clinical and histological characteristics of the CAAG patients studied are detailed in Table 1.

43% of patients presented one or more associated autoimmune diseases, single in 83% of the cases and multiple in 17%. In particular, 49 patients had autoimmune thyroidopathy, four had celiac disease, three had vitiligo, two had Addison's disease, two had undifferentiated connective-tissue disease, one had multiple sclerosis and one myasthenia gravis.

Sixty-five patients (53%) presented with anemia (median value of hemoglobin: 12.3 g/dl; range 4.2–16.0), with a median value of mean corpuscolar volume of 85 fl (range 55–129) and a median anisocytosis index of 14.1% (range 12.3–31.1).

As regards the presence of any micronutrient deficiency, this was detected in 76 patients (62%): single-nutrient deficiency in 24 (32%) and multiple-nutrient deficiency in 52 cases (68%). The median and range values of the micronutrients measured are detailed in Table 2.

In particular, 25-OH vitD deficiency was the main one detected (62% of patients). Median 25-OH vitD levels were significantly lower in the CAAG group than the control group (18 *vs.* 23.9 ng/ml, $p < 0.0001$). Mild 25-OH vitD deficiency, defined as 25-OH vitD levels between 20 and 30 ng/ml, was present in 24 patients (20%), moderate 25-OH vitD deficiency, defined as 25-OH vitD levels between 10 and 20 ng/ml, was present in 35 patients (29%) in the CAAG group. Severe 25-OH vitD deficiency, defined as 25-OH vitD levels lower than 10 ng/ml, was present in 17 patients (14%) in

Table 1
Clinical, epidemiological and histological characteristics of patients with chronic atrophic autoimmune disease.

Patients' characteristics (n = 122)	Data
Sex: F/M (%)	100/22 (82%/18%)
Age: median (range), years	65 (25–90)
Anti-parietal cell antibody: pos/neg (%)	113/9 (93%/7%)
Body mass index: median (range)	24 (17–41)
Blood gastrin levels: median (range)	642 (109–2788) pg/ml
Number of patients with other autoimmune diseases: total (single/multiple diseases)	52 (45/7)
Grading of gastric atrophy: mild/moderate/severe/not known (%)	44/36/21/21 (36%/30%/17%/17%)
Intestinal metaplasia: yes/no (%)	79/43 (65%/35%)
Grading of entero-chromaffin-like cells hyperplasia: absent/linear/micronodular/carcinoid/not known (%)	23/27/27/26/19 (19%/22%/22%/21%/16%)

Table 2
Deficiency of micronutrients in patients with chronic atrophic autoimmune disease.

Micronutrients	No. of patients with deficiency (%)	Median values	Range values
B_{12}	42 (34%)	130 pg/ml	11–190 pg/ml
Folic acid	6 (5%)	3.4 ng/ml	2.9–4.3 ng/ml
25-OH vitamin D	76 (62%)	18 ng/ml	4–35 ng/ml
Ferritin	42 (34%)	14 ng/ml	4–30 ng/ml
Total calcium (Ca^{++})	0 (0%)	9.6 mg/dl (1.2 mmol/L)	5.6–10.7 mg/dl (1.1–2.2 mmol/L)
Phosphate	6 (5%)	3.3 mg/dl	2.1–4.9 mg/dl
Magnesium	3 (2%)	2.1 mg/dl	1.6–4.1 mg/dl

the CAAG group and 148 (12%) patients in the control group. In detail, 25-OH vitD was significantly lower in the CAAG patients as compared with the controls in the age decades 36–45 (17.7 *vs.* 22 ng/ml, p = 0.02), 46–55 (17 *vs.* 22.5 ng/ml, p = 0.03), 56–65 (18.7 *vs.* 24.2 ng/ml, p = 0.0043), 66–75 (17.7 *vs.* 24.3 ng/ml, p < 0.0004) and 76–85 (13.9 *vs.* 24.3 ng/ml, p = 0.003). No differences were observed for the decades below 35 and above 86 years probably because of the low number of CAAG patients in these groups.

Moreover, almost half of the patients with hypovitaminosis D (29 patients, 24% of the CAAG group) had secondary hyperparathyroidism: the median value of PTH was 51 pg/ml (range 16–193 pg/ml) in the CAAG patients. Bone densitometry, which was performed in 40 patients, showed lumbar or femoral osteopenia or osteoporosis in 83% of cases, in 15 and 18 patients respectively: all these patients had hypovitaminosis D and 23 out of them presented hyperparathyroidism; only two patients were aged 40 years or less. Furthermore, among the patients with vitD deficiency 39 (51%) had BMI >25, although there was no statistically significant correlation between 25-OH vitD levels and BMI.

25-OH vitD levels were lower in the patients presenting with a gastric carcinoid rather than in the patients with linear or micronodular ECL cells hyperplasia (11.8 *vs.* 19.8 ng/ml respectively, p-value <0.05) (Fig. 1). Moreover, the patients with CAAG showed a significant correlation between vitamin B_{12} values at diagnosis and 25-OH vitD levels (p = 0.009) (Fig. 2). In detail, the median 25-OH vitD level was 13.9 ng/ml (range 4–49.9) for the patients with vitamin B_{12} deficiency, defined as vitamin B_{12} levels lower than 190 ng/ml.

As regards B_{12} deficiency, it was present in 34% of the cases (42 patients), with a median value of 130 pg/ml. Moreover, B_{12} levels were inversely related to the grading of gastric atrophy (Fig. 3).

As regards iron deficiency, it was present in 34% of the cases, with a ferritin median value of 14 ng/ml: anemia was present in 16 patients.

Finally, there was no significant correlation between B_{12}, folate, ferritin, calcium, magnesium or phosphate levels and BMI, gastrinemia, the grading of gastric atrophy or ECL cells hyperplasia.

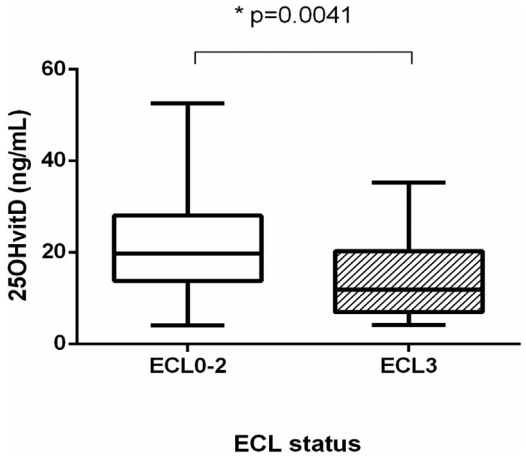

Fig. 1. Inverse correlation between levels of 25-OH vitD and the grading of entero-chromaffin-like (ECL) cells hyperplasia.

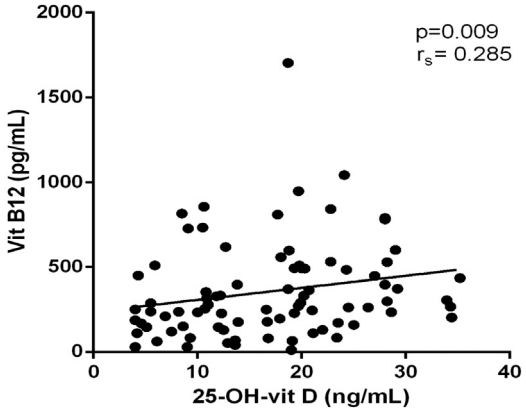

Fig. 2. Direct correlation between 25-OH vitD and B12 levels.

4. Discussion

This study shows that the most frequent vitamin deficiency observed in the CAAG population is 25-OH vitD deficiency, which was present in 62% of our cases and caused secondary hyperparathyroidism in half of the cases, whereas the prevalence of secondary hyperparathyroidism in the general population is 7% [33].

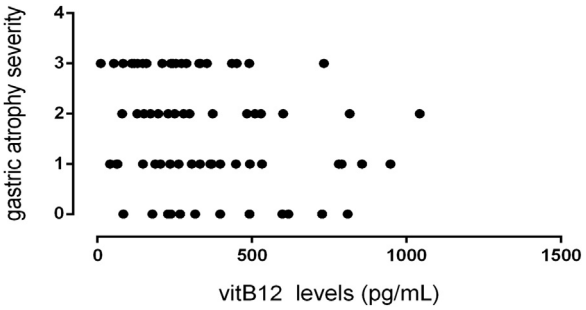

Fig. 3. Inverse correlation between levels of B_{12} and the grading of gastric atrophy.

A limit of this study is that vitamin D levels were not measured in the same season of the year and therefore the result was potentially influenced by recent sunlight exposure. However, this applies to the control group as well.

The increased risk of osteopenia and osteoporosis in patients with gastric achlorhydria represents a well-known issue in the setting of gastric surgery, long-term PPI use and CAAG [34,35]. However, the studies available to date about atrophic gastritis and osteoporosis are few and inconclusive [36–38]. A study by Kim et al. found that atrophic gastritis is associated with osteoporosis in postmenopausal women aged 60 years or older, after adjusting for age, triglycerides, cholesterol, alcohol consumption, and smoking status [39]. However, in our study vitamin D was deficient not only in women aged >60 years, but also in young patients (27 out of 76 patients with vitD deficiency). Moreover, bone densitometry values were altered in most patients undergoing MOC, although other factors, such as the date of menopause for women or previous steroid therapy, may have influenced the T-score or Z-score. Therefore, the presence of altered bone metabolism even in young patients with CAGG suggests a possible association between the two conditions, even if, on the basis of this study alone, it cannot be speculated which is the cause and which the consequence.

Furthermore, although 51% of patients with vitD deficiency had BMI >25, there was no statistically significant correlation between 25-OH vitD levels and BMI. These data seem to be in contrast with what has been previously reported in the literature [40,41]: a possible explanation is that the previous studies have focused on 25-OH vitD levels in predominately overweight or obese women, whereas 76.3% of our patients had BMI <25.

An interesting finding of this study is that B_{12} levels are directly related to those of 25-OH vitD and this indicates the possible presence of underlying common pathogenic mechanisms. Indeed, some *in-vitro* studies have shown the stimulation of osteoclast activity by low vitamin B_{12} concentrations [42].

Furthermore, vitamin B_{12} deficiency is not so common in our series, differently from what reported in the literature. This is possibly explained by the increased use of EGDS in patients with gastroenterological symptoms and therefore due to the earlier diagnosis of CAAG compared to what happened in the past. It is well known that pernicious anemia tends to appear around the age of 60 years and in our case one third of our CAAG patients was aged <60 years. Furthermore, since the data on olotranscobalamin, serum homocysteine and methylmalonic acid was not available, and considering a lower limit normal of 190 pg/ml for vitamin B_{12}, B_{12} deficiency have been possibly underestimated.

As regards the presence of low ferritin levels, we have observed the same prevalence of B_{12} deficiency, in accordance with what has been already reported in the literature. Indeed, several studies have observed iron deficiency especially in patients with early CAAG diagnosis, since IDA is possibly one of the first manifestations of this disease and precedes the onset of pernicious anemia. This trend also seems to be confirmed by our study.

Instead, the prevalence of phosphate and magnesium deficiency was very low in the CAAG patients, being 5% and 2%, respectively, whereas hypocalcemia was detected in no patients, although these data were probably affected by the small size of the sample studied.

Moreover, a limit of this study is that it is not possible to establish with certainty the actual age of onset of the disease, thus possibly influencing the final data on micronutrient deficiencies.

As concerns the finding of vitamin D deficiency, only a previous study by Antico et al. had investigated vitD levels in the patients with CAAG, reporting average values of 9.8 ± 5.6 ng/ml and hypothesizing that this deficit would potentially play a decisive role in the pathogenesis of CAAG [43]. Indeed, according to the literature the possible role of vitD deficiency in the pathogenesis of autoimmune diseases has recently emerged. Experimental studies have shown that VDR agonists promote the proliferation of dendritic cells capable of inducing tolerance, stimulating the differentiation of CD4+ CD25+ regulating T-lymphocytes and thus blocking the development of type-1 *diabetes mellitus* [44]. Vitamin D modulates the immune system, directly regulating the functions of B and T-lymphocytes and inhibiting the differentiation and maturation of dendritic cells, which are essential for inducing self-tolerance. In fact, the presentation of an antigen to T-cells by mature dendritic cells stimulates an immune response against the antigen, while the presentation by immature dendritic cells facilitates the tolerance mechanism [45]. Therefore, one may assume that vitamin D deficiency may also play a role in the onset and development of CAAG, although further studies are needed to confirm this hypothesis.

Furthermore, the anti-proliferative effect of vitamin D, already described in the literature [46], possibly explains the presence of lower levels of vitamin D in patients with gastric carcinoids. A recent study has shown the frequent presence of vitD deficiency in patients with neuroendocrine tumors of the gastro-entero-pancreatic tract [47]. Furthermore, another study has observed that neuroendocrine cells express VDR and that an analog of 1,25-(OH)2 vitD is able to induce the cell-cycle arrest in the G0/G1 phase and apoptosis in a murine insulinoma cell line. Further studies, both *in vitro* and *in vivo*, would be useful to confirm the possible role of vitD deficiency in the pathogenensis of gastric carcinoids.

In conclusion, this study highlights the high prevalence of vitamin or oligoelements deficiency, especially of vitamin D, in patients with CAAG, suggesting the possible pathogenic role of vitD deficiency in the onset and development of CAAG. Therefore, the routine evaluation of these deficiencies and adequate supplementation are appropriate. However, given the small sample size of this study, further larger studies are needed to confirm this observation and to evaluate if vitamin D supplementation can lessen the destruction of gastric parietal cells.

Conflict of interest

Non declared.

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