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Study of Chronic Atrophic Gastritis in Patients with Autoimmune Thyroid Disease

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ABSTRACT

Background: Patients with autoimmune thyroid disease (ATD) may have a greater frequency of anti-parietal cell antibodies (APCA) than the general population.

Objective: The study's goal is to look at chronic atrophic gastritis in people who have autoimmune thyroid illness.

Patients and Methods: In 60 ATD patients, APCA was detected using an indirect immunofluorescence test: 33(55%) had Graves' disease and 27(45%) had Hashimoto's thyroiditis. A systematic questionnaire was used to assess gastrointestinal symptoms, prior history of thrombosis, arthralgia, and other autoimmune disorders in patients and their families. Individuals with both positive and negative APCA were compared. Patients who tested positive were encouraged to have upper gastrointestinal endoscopy and numerous biopsies of the antral, body angular, and prepyloric segments performed. As controls, sera from 30 healthy people hailing from the same geographic region were utilized.

Results: APCA was found in 20% (12/60) of ATD patients, including 21.3 percent (7/33) in the Graves' group and 18.6 percent (5/27) in the Hashimoto's sample (P = 0.796). Positive APCA patients exhibited greater anemia (P > 0.001) and reduced heartburn and epigastric discomfort (P = 0.002&0.004, respectively). A total of 66.7 percent of the 12 APCA-positive patients who underwent upper endoscopy exhibited chronic atrophic gastritis.

Conclusion: ATD patients have a significant prevalence of positive APCA. APCA are more frequent in people who have anemia and much less in those suffering heartburn or epigastric discomfort. Approximately 66.7 percent of APCA-positive individuals had chronic atrophic gastritis.

Keywords: *Anti-parietal cells; Thyroiditis; Autoimmunity.*

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INTRODUCTION

Atrophic gastritis (AG) is a chronic inflammation of the stomach mucosa characterized by the loss of gastric glandular cells and the replacement of these cells via intestinal type epithelium, pyloric type glands, and fibrous tissue. Chronic mechanisms, like chronic gastritis related to Helicobacter pylori (H. pylori) infection, lead to atrophy of the stomach mucosa, reactive gastropathy and autoimmunity directed against gastric glandular cells.[1]

More than 10 percent of AG patients suffer predisposition to develop gastric carcinoid and adenocarcinoma as a result of chronic hypergastrinemia caused by achlorhydria and subsequent enterochromaffin-like cells neoplastic transformation.[2]

The hallmark of pernicious anemia, a consequence of autoimmune metaplastic atrophic gastritis (AMAG), is the anti-parietal cell antibodies (APCA), considered to be highly sensible for this disease.[3]

They are found between 85 and 90% of pernicious anemia patients but their presence is not enough for diagnosis, as they aren't special for that disorder. Antibodies to these proteins are also detected in 7.8% to 19.5 percent of seemingly healthy adults.[4]

The issue of whether H. pylori infection is linked to the existence of APCA is intriguing and not well understood.[5] APCA is identified in 6.1 percent to 20.7 percent of these individuals, and it has been suggested that this infectious pathogen is an etiologic AMAG agent.[4,6]

Autoimmune diseases may occur in groups in the same person. It's debatable whether this grouping is due to a common genetic background or being exposed to a common trigger. A raised frequency of AMAG in diabetics of type 1 diabetes mellitus, vitiligo, celiac disease…etc. has been observed, also T1DM and AMAG often occurs together.[7,8]

PATIENTS AND METHODS

This prospective matched controlled study involved 90 subjects (60 ATD patients, 30 healthy subjects) were conducted in the outpatient endocrinology clinics, Internal Medicine department at Bab-El-Shaaryia and El-Hussein hospitals Al-Azhar University during the period from Mar –2019 to Dec -2020.

The following were excluded from the study: Patients with other thyroid disorders (cancer thyroid and thyroid surgery), parathyroid disorders (hypo or hyperparathyroidism), other endocrinological disorders (e.g.DM, Addison's disease), active malignancies, chronic liver or kidney disease, autoimmune GIT disorders as ulcerative colitis and active or severe infection.

All patients were subjected to: Detailed history taking: Age and sex, symptoms of thyroid dysfunction, symptoms suggest other endocrinological disorders, a systematic questionnaire for symptoms of the gastrointestinal tract and prior history of (thrombosis, arthralgia as well as other autoimmune disorders among family and themselves).

Full clinical examination including: Full thyroid, cardiovascular, chest, abdominal and neurological examination to evaluate other systems and to exclude patients with other system affection.

Laboratory investigations: CBC, ALT, AST, PT, INR, serum albumin, bilirubin, creatinine, FPG, Hb-A1c, TC, TG, LDL-C, HDL-C and serum calcium.

Assessment of autoimmune thyroid disease: Thyroid ultrasound, thyroid functions (TSH, FT3 and FT4), thyroid stimulating immunoglobulins and thyroid peroxidase antibodies .

Assessment of chronic atrophic gastritis: Astructured questionnaire for GIT symptoms, anti-parietal cell antibodies, helicobacter pylori antigen in stool and upper endoscope with biopsies for histopathological assessment for patients with positive APCA.

Ethical consideration: The nature of the study was explained to all participants fulfilling the above-mentioned criteria and a verbal consent was obtained.

Statistical analysis: Frequency and contingency statistics were gathered. The Kolmogorov–Smirnov test was used to assess the distribution; central tendency was represented as median and interquartile range (IQR), as well as mean and standard deviation (SD). Patients were split into two groups: those who were APCA positive and those who were APCA negative, and they were compared amongst themselves: the whole group as well as the Graves' and Hashimoto's thyroiditis groups individually. Fisher's and Chi-squared tests were used to compare numeric data, while Mann–Whitney and unpaired t tests were used to compare numerical data. The chosen significance level was 5%.

RESULTS

The study included: Group I: 60 patients with ATD disorders (Graves' disease 33 patients 28 females and 5 males with positive thyroid stimulating immunoglobulins) and (Hashimoto's thyroiditis 27 patients 24 females and 3 males with positive thyroid peroxidase antibodies). Group II: 30 healthy subjects (control group) 27 females and 3 males.

The prevalence of APCA positive was 12/60 (20%) in the ATD patients examined, compared to 1/30 (3.3%) in the healthy controls (P = 0.034). The titers of APCA positivity in ATD patients varied from 1:80 to 1:320, with 2/12 (16.6 percent) having low titers, 3/12 (25 percent) having moderate titers, and 7/12 (58.4%) having high titers. APCA was found in 7/33 (21.3%) Graves' patients, while Hashimoto's thyroiditis was found in 5/27 (18.6%) (P = 0.796). There were no differences in median titers between the two groups (P = 0.929).

There is statistically significant increase in anemia (P < 0.01) and less complaints of heart burn and epigastric pain (P = 0.002& 0.004 respectively) in ATD patients with positive APCA than negative (Table: 1).

There is statistically significant increase in anemia (P = 0.021) and less complaints of heart burn and epigastric pain (P = 0.030& 0.041respectively) in Graves' disease patients with positive APCA than negative (Table: 2).

There is statistically significant increase in anemia (P = 0.002) and less complaints of heart burn and epigastric pain (P = 0.028& 0.048 respectively) in patients of Hashimoto's thyroiditis and having positive APCA than negative (Table: 3).

In APCA-positive patients with upper gastrointestinal endoscope there was H. pylori infection 3/12 (25%), atrophic gastritis 1/12 (8.3%), H. pylori infection with signs of atrophic gastritis 7/12 (58.4%), no H. pylori infection or signs of atrophic gastritis 1/12 (8.3%), H. pylori-positive patients 10/12 (83.4%) and atrophic gastritis-positive patients 8/12 (66.7%) (Table: 4).

There is statistically significant difference between H. pylori-positive and negative patients as regard APCA titers (P = 0.002, Table:5)

There is a statistically significant variation among atrophic gastritis-positive and negative patients as regard APCA titers (P = 0.011, Table:6)

Variable	All ATD patients No. = 60	ATD with positive APCA N = 12 (20%)	ATD without APCA N = 48 (80%)	Test value	P-value	Sig.
Sex Female gender Male gender	 52 (86.6%) 8 (13.4%)	 10 (83.3%) 2 (16.7%)	 42 (87.5%) 6 (12.5%)	0.144*	0.704	NS
Age (years) Mean ± SD Range	 53.87 ± 8.30 15 – 75	 54.20 ± 8.71 16 – 75	 53.16 ± 8.83 15 – 74	-0.373•	0.710	NS
Anemia	9 (15.0%)	6 (50.0%)	3 (6.3%)	14.412*	0.000	HS
Epigastric pain	32 (53.3%)	2 (16.7%)	30 (62.5%)	8.103*	0.004	HS
Abdominal pain	16 (26.7%)	3 (25.0%)	13 (27.1%)	0.021*	0.885	NS
Bloating	28 (46.7%)	6 (50.0%)	22 (45.9%)	0.067*	0.796	NS
Heartburn	40 (66.7%)	3 (25.0%)	35 (72.9%)	9.492*	0.002	HS
Dyspepsia	13 (21.7%)	2 (16.7%)	11 (23.0%)	0.221*	0.638	NS
Diarrhea	9 (15.0%)	2 (16.7%)	7 (14.6%)	0.033*	0.856	NS
Constipation	21 (35.0%)	5 (41.7%)	16 (33.4%)	0.293*	0.588	NS
Arthralgia	37 (61.7%)	7 (58.4%)	30 (62.5%)	0.071*	0.790	NS
Skin disease (†)	7 (11.7%)	2 (16.7%)	5 (10.5%)	0.364*	0.546	NS
Thrombosis	2 (3.4%)	1 (8.4%)	1 (2.1%)	1.164*	0.281	NS
Other autoimmune diseases (††)	7 (11.7%)	2 (16.7%)	5 (10.5%)	0.364*	0.546	NS
Family history of autoimmune diseases	25 (41.7%)	5 (41.7%)	20 (41.7%)	0.000*	1.000	NS

Table 1: Compare all ATD patients with and without APCA.

	Graves' disease (N = 33) (55%)		Test value	P-value	Sig.
	APCA positive (n = 7) (21.3%)	APCA negative (n = 26) (78.7%)			
Sex Female gender Male gender	 6 (85.7%) 1 (14.3%)	 22 (84.6%) 4 (15.4%)	0.005*	0.944	NS
Age (years) Mean ± SD Range	 55.93 ± 8.51 17 – 75	 54.36 ± 9.13 16 – 74	-0.409•	0.685	NS
Anemia	3 (42.9%)	2 (7.7%)	5.305*	0.021	S
Epigastric pain	1 (14.3%)	15 (57.7%)	4.160*	0.041	S
Heartburn	2 (28.6%)	19 (73.1%)	4.721*	0.030	S

Table 2: Comparison between Graves' disease patients with and without APCA.

	Hashimoto's thyroiditis (N = 27) (45%)		Test value	P-value	Sig.
	APCA positive (n = 5) (18.6%)	APCA negative (n = 22) (81.4%)			
Sex Female gender Male gender	 4 (80.0%) 1 (20.0%)	 20 (90.9%) 2 (9.1%)	0.491*	0.483	NS
Age (years) Mean ± SD Range	 56.25 ± 9.60 16 – 74	 54.91 ± 9.72 15 – 73	-0.279•	0.783	NS
Anemia	3 (60.0%)	1 (4.5%)	9.928*	0.002	HS
Epigastric pain	1 (20.0%)	15 (68.2%)	3.918*	0.048	S
Heartburn	1 (20.0%)	16 (72.7%)	4.857*	0.028	S
Daily levothyroxine (mcg/kg) Median (IQR)	 2.55 (2.31–3.07)	 1.48 (1.15–1.89)	-2.247≠	0.023	S

Table 3: Comparison between Hashimoto's thyroiditis patients with and without APCA.

Number	3/12 (25%)	2/12 (16.7%)	1/12 (8.3%)	4/12 (33.4%)	7/12 (58.4%)	1/12 (8.3%)
Upper endoscope with biopsy	H. pylori+ve	H. pylori –ve	AG +ve	AG –ve	H. pylori+ve + AG +ve	No H. pylorior AG

Table 4: APCA-positive patients with upper gastrointestinal endoscope with biopsy.

APCA Titer	Low Titer	Moderate Titer	High Titer	Test value	P-value	Sig.
H. pylori +ve Patients	0/10 (0%)	3/10 (30%)	7/10 (70%)	12.000	0.002	HS
H. pylori –ve Patients	2/2 (100%)	0/2 (0%)	0/2 (0%)			

Table 5: Compare APCA titers in H. pylori-positive and negative patients.

APCA Titer	Low Titer	Moderate Titer	High Titer	Test value	P-value	Sig.
AG +ve Patients	0/8 (0.0%)	1/8 (12.5%)	7/8 (87.5%)	9.000	0.011	S
AG –ve Patients	2/4 (50%)	2/4 (50.0%)	0/4 (0%)			

Table 6: Compare APCA titers in atrophic gastritis-positive and negative patients.

DISCUSSION

This study has discovered a significant elevated prevalence of APCA 20% for ATD patients in contrast with normal control (P = 0.034).

Autoimmune disorders aside from autoimmune atrophic gastritis and ATD discovered being linked not only in this patient group (11.7%) but also in their families (41.7%) (P = 0.546& 1.000 respectively, table:1).

The current study agrees with study done by *Fallahi et al., (2016)*[9] which documented that the autoimmune syndromes have a tendency to cluster in the same patient.

The current study discovered that APCA frequency in ATD patients was 20% which is significantly higher than in normal control (3.3%) (P = 0.034). This result agrees with *Garcia-Garcia et al., (2010)*[10] which mentioned that the frequency of APCA was 20% in 148 ATD patients from Spain.

On the other hand, study done by *Centanni et al., (1999)*[11] reported that a higher prevalence of APCA which was 40% in their 62 ATD patients in Italy. These results were higher than the current study. This difference may be due to variances in the commonness of co-existence of H. pylori infection and exposure to risk factors in their study compared to the current study.

In the present study anemia stood as the main clinical mark that linked with autoimmune atrophic gastritis in an ATD patient. Occurrence of anemia was significantly high in ATD patients with positive anti-parietal cell antibodies in comparison to ATD patients without anti-parietal cell antibodies (P < 0.001, table:3). This result was in agreement with *Sibilla et al., (2008)*[12] who reported that the prevalence of anemia was significantly elevated in ATD patients associated with other autoimmune diseases rather than in those with plain ATD.

Wu et al., (2017)[13] discussed that Anemia in ATD patients with positive APCA was due to APCA may cause the death of stomach parietal cells, leading in intrinsic factor failure. Intrinsic factor insufficiency can lead to inadequate vitamin B12 absorption, which can lead to pernicious anemia.

Also; *Lopez et al., (2016)*[14] reported that Iron deficiency may lead to anemia in this scenario since iron is absorbed at finest in acidic conditions.

In the current study a contrast between positive and negative APCA in both Graves' and Hashimoto's thyroiditis groups there were highly significant increase in occurrence of anemia in positive APCA in both Graves' and Hashimoto's thyroiditis groups in comparison to negative groups (P = 0.021& 0.002 respectively, tables:2,3).

On contrast, *Sibilla et al., (2008)*[12] stated that anemia in ATD patients was more prevalent in patients with hypothyroidism. Those results were contrary to *De Carvalho et al., (2018)*[15] who mentioned that anemia can be proved to be linked to Graves' patients. These results were different from the current study in which anemia might be evidenced to be related to both Graves' and Hashimoto's thyroiditis patients. This difference may be due to a high occurrence of APCA in both Graves' and Hashimoto's thyroiditis groups in the current study.

In the current study there is another remarkable finding: patients with ATD who were positive for APCA had significantly less gastrointestinal issues (heart burn and epigastric pain) than those who were negative for these autoantibodies (P = 0.002& 0.004 respectively, table:1).

These results agree with *Utiyama et al., (2017)*[16] who found that ATD patients having positive APCA had lower gastrointestinal complaints (heart burn and epigastric pain) than those with negative for these autoantibodies. They attributed the low prevalence of heartburn and epigastric pain to the lesser acidic environment detected in patients of ATD and suffering atrophic gastritis.

As regards; study of APCA positive patients in this study by upper endoscopy, biopsy and test for H pylori the results show that 66.7% of APCA positive patients had autoimmune atrophic gastritis (Table: 4). This result matched with study done by *De Carvalho et al., (2018)*[15] who mentioned that more than half of studied APCA positive patients had autoimmune atrophic gastritis.

According to Tozzoli et al., *(2010)*[17] who followed prospectively 25 ATD patients who were APCA positive and discovered that 24 percent of them developed auto - immune gastritis within 5 years, it's probable that a few of the tested subjects who had negative for autoimmune gastritis will develop the disease in the future. As a result, a follow-up with ATD patients who have positive APCA will aid in elucidating this feature.

The link between H. pylori infection and autoimmune atrophic gastritis in positive APCA is debated. About 58.4% of patients in the current study with biopsy-proven autoimmune atrophic gastritis also had H. pylori infection (Table: 4). As well, this result was close to study done by *Utiyama et al., (2017)*[16] who reported that about 60 percent of their patients having biopsy-proven ATD and suffer H. pylori infection.

The current research, no statistically significant difference was found between Graves' disease and Hashimoto's thyroiditis patients regarding APCA titers (P = 0.929).This result agrees with *Venerito et al.,(2015)*[7] who found that there is no difference between Graves' disease and Hashimoto's thyroiditis patients regarding APCA titers in their 83 patients of ATD in Italy.

On the other hand, in positive APCA patients there was relation to H pylori: The titers of APCA in H. pylori-positive was moderate titers in 3/10 (30%) and high titers in 7/10 (70%) while in H. pylori-negative there was low titers in 2/2 (100%). The titers of APCA were statistically highly significant increase in H. pylori-positive patients than negative (P = 0.002, table:5).

Also, a statistically significant increase titers of APCA was detected in atrophic gastritis: The titers of APCA in atrophic gastritis-positive patients was moderate titers in 1/8 (12.5%) and high titers in 7/8 (87.5%) while in atrophic gastritis-negative patients it was low titers in 2/4 (50%) and moderate titers in 2/4 (50%) (P = 0.011, table:6).

However, this observation did not match with *Utiyama et al., (2017)*[16] who found that a statistically significant difference doesn't exist between H. pylori infected patients and atrophic gastritis-positive and negative patients. Also, they reported that no statistically significant difference between titers of APCA and atrophic gastritis. This difference may be attributed to that only half of the selected patients in that study undergo upper endoscopy. While all the studied patients in this study undergo upper endoscopy.

In the current study there was significantly increase daily requirement of levothyroxine in Hashimoto's thyroiditis APCA positive patients in comparison to negatives APCA (P = 0.023, table:3). This result agrees with *Gerenova et al., (2013)*[18] who mentioned that an APCA commonness of 33.8% in Hashimoto's thyroiditis and that the positive patients needed a cure with an increased dosage of levothyroxine rather than the negatives.

CONCLUSION

ATD patients have a significant prevalence of positive APCA. APCA are more frequent in people who have anaemia, and they are lesser among those who have heartburn or epigastric discomfort. About 66.7 percent of those who tested positive for the APCA developed chronic atrophic gastritis.

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