Endocr (2010) 38:199–205
DOI 10.1007/s12020-010-9373-x

ORIGINAL ARTICLE

A comparison of antineutrophil cytoplasmic antibody prevalence in patients treated and untreated for hyperthyroidism

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Received: 18 February 2010 / Accepted: 1 July 2010 / Published online: 11 July 2010

Abstract We aimed to compare the prevalence of antineutrophil cytoplasmic antibody (ANCA) and its subgroups between on-treatment (with anti-thyroid drugs; propylthiouracil, methimazole) and untreated patients with hyperthyroidism in our unit. Overall 78 consecutive patients were enrolled in the study; 45 patients were on-treatment (female/male 31:14) and 33 were newly diagnosed (female/male 20:13). We have studied ANCA, perinuclear-ANCA (p-ANCA), cytoplasmic-ANCA (c-ANCA), myeloperoxidase-ANCA (mpo-ANCA), and proteinase 3-ANCA (pr3-ANCA) in sera of all the patients. The data about clinical status, laboratory tests, and physical examination and mean duration of treatment in treated group were recorded. There was no statistically significant difference between the two groups for ANCA, c-ANCA, and pr3-ANCA ($P = 0.13$, $P = 0.07$, and $P = 0.63$ respectively). p-ANCA and mpo-ANCA prevalences were significantly higher in on-treatment group than in untreated group ($P = 0.04$ and $P = 0.01$, respectively). The mean duration of treatment was 17 months in on-treatment group. The use of antithyroid drugs (propylthiouracil, methimazole) seems to be correlated with increased prevalence of ANCA. These drugs may especially increase p-ANCA and mpo-ANCA positivity.

Keywords ANCA prevalence · Propylthiouracil · Methimazole · p-ANCA · c-ANCA

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Introduction

Hyperthyroidism is a hypermetabolic condition characterized by increased levels of free T3 or free T4 or both. The most common cause of hyperthyroidism is Graves' disease (50–60%) [1]. Antithyroid drugs have been in widespread use since 1940s. Propylthiouracil (PTU) and methimazole (MMI) are used in Turkey as antithyroid drugs.

Antithyroid drugs have several adverse effects, the most common of which are allergic reactions such as fever, weakness, rash, urticaria, and arthralgia observed in 1–5% of patients during the first few weeks of treatment. Agranulocytosis, aplastic anemia, hepatitis, polyarthritis, and lupus-like vasculitis may occur as more severe adverse reactions. When these adverse reactions are observed antithyroid drugs might be discontinued. In addition, antineutrophil cytoplasmic antibody (ANCA) positivity, ANCA-positive vasculitis, and ANCA-positive pyoderma gangrenosum have also been reported in association with PTU [2–7]. The development of central nervous system vasculitis with MMI treatment has also been described, resolving completely 6 months after cessation of treatment [8]. Other studies have reported alveolar hemorrhage and interstitial pneumonia following treatment with antithyroid medication [9–11].

ANCAs are a group of autoantibodies that are formed against proteins in the peroxidase-positive lysosomes of monocytes in neutrophil granulocytes and peripheral blood. They are mainly IgG-type antibodies. ANCA positivity is observed in small vessel vasculitis, i.e., microscopic polyarteritis (MPA). Wegener's granulomatosis (WG), Churg–Strauss syndrome (CSS), and types of drug-associated vasculitis constitute the ANCA-positive vasculitis group. ANCAs may be perinuclear (p-ANCA) or cytoplasmic (c-ANCA), depending on localization in the cytoplasm. c-ANCAs are mainly formed against the proteinase 3 (PR-3) antigen, a serine protease contained in azurophilic granules of neutrophils, and they display a cytoplasmic-granular immunofluorescent staining pattern. p-ANCAs, on the other hand, may develop against various antigens [myeloperoxidase (MPO), lactoferrin, elastase, cathepsin G, alpha enolase, beta- glucuronidase, bactericidal/permeability-increasing protein (BPI), lysozyme]. Most important of these is the ANCA against myeloperoxidase (mpo-ANCA), which displays perinuclear or nuclear staining pattern [12].

ANCA-positive vasculitis is a rare complication of antithyroid drug treatment [11, 13–21]. ANCA-positive vasculitis associated with antithyroid drug treatment was first described in 1992 [17]. Although the suspected drug was PTU in about 90% of cases [22], vasculitis development with MMI has also been reported [18]. Graves' disease is the most frequent underlying thyroid disease in patients with ANCA-positive vasculitis associated with antithyroid medication [8, 11, 16, 18, 23]. On the other hand, ANCA positivity and ANCA-positive vasculitis have also been described for patients diagnosed with toxic multinodular goiter who were receiving antithyroid drug treatment [5, 22].

Repetitive and intermittent treatments with antithyroid medication have been described as a risk factor for ANCA positivity [7]. Decreases in ANCA titers are typically observed following cessation of drug which causes ANCA positivity, but ANCA positivity may persist for months and years in some patients. The length of treatment with antithyroid drugs has also been cited as a factor increasing the risk of ANCA positivity [22, 24].

The ANCA assay is a very helpful tool for the clinician in terms of diagnoses and differential diagnosis of several autoimmune diseases. In a study monitoring patients who developed vasculitis following antithyroid treatment, a significant reduction in ANCA titers was demonstrated after treatment of vasculitis, while an increase was also reported in some patients, despite the absence of an apparent vasculitis relapse [25]. Another study reported significant increases in ANCA titers prior to all relapses and ANCA titers increased in one patient without a clinically relevant sign [26].

ANCA positivity after diagnosis of hyperthyroidism and treatment with antithyroid drugs (MMI, PTU) has been reported by several studies in the literature [3, 5–7, 10, 27, 28]. A literature review for studies in English and Turkish languages did not reveal any controlled studies performed and published in Turkey on the incidence of ANCA in patients receiving and not receiving antithyroid treatment. This study aims to compare newly diagnosed Turkish patients with hyperthyroidism and patients with hyperthyroidism who have been receiving uninterrupted antithyroid medication (PTU, MMI) for at least 6 months in terms of ANCA frequency.

Patients and methods

Overall, 78 consecutive patients were enrolled in the study: 45 patients who had received antithyroid treatment (female/male 31:14) and 33 newly diagnosed with hyperthyroidism (female/male 20:13). The patient was diagnosed as hyperthyroid when s/he has hypermetabolic symptoms along with high serum-free T3 and/or T4 and low TSH levels. Patients were selected from among patients referred to the outpatient clinic of Istanbul University Cerrahpaşa Faculty of Medicine Endocrinology and Metabolism Department between December 2007 and July 2008. One-to-one meetings were carried out with each patient who met the inclusion criteria, and the selected individuals were enrolled in the study after providing informed consents. To be included in the study group, the patients were required to have been receiving antithyroid drug treatment (MMI or PTU) for at least 6 months, not to have previously received an immunosuppressive treatment, not to have been diagnosed with Wegener's granulomatosis, polyarteritis nodosa, or microscopic polyarteritis, Churg–Strauss syndrome (CSS), inflammatory bowel disease, autoimmune hepatitis, rheumatoid arthritis or any malignancy, not to have any active infections during the study period and to be 18–65 years of age. We aimed to compare the prevalence of ANCA and its subgroups between on-treatment (with anti-thyroid drugs; propylthiouracil, methimazole) and untreated patients with hyperthyroidism in our unit. Inclusion criteria for untreated group were as follows: not to have received an antithyroid drug treatment previously, not to have any of the disorders mentioned above, and to be 18–65 years of age.

Based on detailed analysis of history and laboratory findings, the patients underwent comprehensive evaluation for fulfilling the inclusion criteria. The group of subjects with diagnosed hyperthyroidism who had received previous antithyroid drug treatment underwent a further, detailed retrospective evaluation of medical records to determine whether they complied with the inclusion

criteria. Each patient was monitored by means of individual follow-up records.

Technical data and statistics

Ten milliliters of venous blood was collected from each patient in plain (no additive) blood tubes in the morning following an 8-h fasting. All blood samples of the subjects in each group were centrifuged for 10 min at 2,000 rpm, and the obtained serum samples were placed in four different tubes and stored at −80°C. Once the targeted number of patients was reached, all the serum samples were studied simultaneously.

Two different techniques were used in the study: Indirect Immunofluorescence Assay (IFA) and Enzyme-Linked Immunosorbent Assay (ELISA). Kits analyzed with IFA (ImmuGlo—IMMCO Diagnostic, Buffalo, NY, USA) were used for p-ANCA and c-ANCA assays, and kits analyzed with micro-ELISA (ImmuLisa—IMMCO Diagnostic, Buffalo, NY, USA) were used for anti-MPO and anti-PR3 assays for ANCA subgroups. Standards and controls contained in the kits and the serum samples which had been placed in tubes and stored at −80°C were heated to room temperature.

The study was planned as a cross-sectional observational cohort study. The primary outcome of the study was ANCA frequency in both the groups.

A sample size of 33 patients per group was determined to be sufficient to detect, with 80% power, a 32% difference between on-treatment and untreated groups. A P value of less than 0.05 was considered to indicate statistical significance, and all tests were two-sided. ANOVA was used for continuous variables and the results were presented as mean ± standard deviation (mean ± SD). A Chi-square test (χ^2) was used for categorical variables. Statistical evaluation of the obtained data was carried out using SPSS v.13.00 for Windows (SPSS, Inc, Chicago, IL, USA).

This study was approved by the local ethics board and supported by the research projects fund unit of Istanbul University.

Results

Mean age of patients with hyperthyroidism enrolled in the study was 43 ± 13 for on-treatment group, and 41 ± 16 for the untreated group. There were 45 subjects in the on-treatment group, of which 14 were males and 31 were females. There were 33 subjects in the untreated group, of which 13 were males and 20 were females. Patients' diagnoses are shown in Table 1.

Mean period of drug treatment in the on-treatment group was 17 ± 16 months. Four patients used MMI and 41 used PTU.

There were no significant differences between the two groups in terms of age, sex, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sedimentation, or C-reactive protein (CRP) values. The comparison of the two groups by demographic and laboratory values is shown in Table 2. There was no statistically significant difference between the number of male and female subjects with ANCA positivity in the on-treatment group (ANCA positivity: 8/14 for males and 16/31 for females, $P = 0.3$), and in the untreated group ($P = 0.6$).

Although the difference was not statistically significant a comparison of ANCA positivity in the two groups revealed a higher frequency in the on-treatment group when compared to the untreated group (53 vs. 36%; P= 0.13) (Table 3).

The distribution and comparison of ANCA and ANCA subgroups in the two groups are shown in Table 3.

Comparison of the two groups revealed a significantly higher frequency of p-ANCA positivity in the on-treatment group ($P = 0.04$).

c-ANCA was positive in 3 out of 33 patients in the untreated patients (3/33, 9%). pr3-ANCA was not positive in any of these 3 patients. However, a pr3-ANCA positivity was obtained for one c-ANCA negative patient. In the on-treatment group, c-ANCA was not positive in any of the subjects (0/45, 0%). On the other hand, pr3-ANCA positivity was detected in 3 of these patients. There were no significant differences between the two

Table 1 Distribution of subjects in both groups by diagnosis

Group	Untreated group ($n = 33$)		On-treatment group ($n = 45$)		
	Autoimmune	Non-autoimmune	Autoimmune	Non-autoimmune	Unknown diagnose
	Graves: 20	MNG: 10	Graves: 34	TA: 4	1
	Hashimoto: 1	TA: 1		MNG: 6	
		GTT: 1			
Total	21	12	34	10	1

MNG multinodular goiter, *TA* toxic adenoma, *GTT* gestational thyrotoxicosis

Table 2 Comparison of the two groups by demographic and laboratory values

	Untreated group		On-treatment group		*P*
	Mean	SD	Mean	SD	
Age (year)	41	16	43	13	0.5
TSH (μIU/ml)	0.004	0.007	1.133	1.586	<0.001
FT3 (ng/dl)	13.88	12.89	4.15	3.900	<0.001
FT4 (ng/dl)	2.896	1.551	1.415	1.585	<0.001
AST (U/l)	19	5	18	5	0.5
ALT (U/l)	23	9	22	12	0.3

FT3 free T3, *FT4* free T4, *SD* standard deviation, *TSH* thyroid stimulant hormone, *ALT* alanine transaminase, *AST* aspartate transaminase

Table 3 Distribution and comparison of ANCA and ANCA subgroups in the two groups

	Untreated group ($n = 33$)	On-treatment group ($n = 45$)	*P*
ANCA (+)	12 (36%)	24 (53%)	0.13
p-ANCA (+)	10 (30%)	24 (53%)	0.04
mpo-ANCA (+)	0 (0%)	7 (16%)	0.018
c-ANCA (+)	3 (9%)	0 (0%)	0.07
pr3-ANCA (+)	1 (3%)	3 (7%)	0.63

ANCA antineutrophil cytoplasmic antibody, *p-ANCA* perinuclear ANCA, *mpo-ANCA* myeloperoxidase ANCA, *c-ANCA* cytoplasmic ANCA, *pr3-ANCA* proteinase 3 ANCA

groups in c-ANCA or pr3-ANCA frequency ($P = 0.07$, $P = 0.63$ respectively).

p-ANCA was positive in 21 of patients using PTU (21/41, 51%). mpo-ANCA was positive in only 7 of these 21 patients. c-ANCA was not positive in any of the patients in the PTU group, while pr3-ANCA was positive in 3.

p-ANCA was positive in 3 out of 4 patients using MMI. One of these 3 patients was also mpo-ANCA positive. c-ANCA and pr3-ANCA were negative in all the patients in the group using MMI.

Comparison of patients with hyperthyroidism who have and have not received drug therapy in terms of mpo-ANCA, a subgroup of p-ANCA, showed significantly higher frequency of mpo-ANCA in the on-treatment group ($P = 0.018$) (Table 3).

A subgroup analysis covering only those subjects with Graves' disease (p-ANCA was positive in 16/34 and in 7/20 patients in the on-treatment and untreated group, respectively) did not reveal a statistically significant difference for p-ANCA positivity between the two groups ($P = 0.38$).

When the total frequency of ANCA was examined in terms of non-autoimmune thyroid diseases between the two groups, ANCA frequency was significantly higher in on-treatment group (8/10, 80%) than in untreated group (4/12, 33%) ($P = 0.04$).

Comparison of the two groups for p-ANCA regarding only non-autoimmune thyroid diseases revealed a significantly higher frequency of p-ANCA in the on-treatment group ($P = 0.008$). An analysis of mpo-ANCA, c-ANCA, and pr3-ANCA in the same regard showed no statistically significant differences between the two groups ($P = 0.45$, $P = 0.48$, and $P = 0.57$, respectively).

Discussion and conclusion

The frequency of ANCA in patients receiving antithyroid drug treatment has been investigated in a limited number of studies which reported different frequencies. The number of studies comparing ANCA positivity in patients who receive and do not receive antithyroid drug treatment is even less. In this study, we aimed to compare ANCA positivity in 45 patients who had been treated with antithyroid drugs (PTU, MMI) and 33 patients without any previous treatment with antithyroid drugs, both diagnosed with hyperthyroidism.

A high frequency of ANCA positivity has been reported in patients receiving treatment with antithyroid medication [22, 27, 29]. Both antithyroid drugs may lead to asymptomatic ANCA positivity, but PTU is the agent which causes most frequent ANCA positivity [22, 23, 29].

Previous studies have described that ANCA positivity may occur weeks, months, and even years after initiation of antithyroid drug treatment [8, 30, 31]. The mean duration of antithyroid drug treatment in our study was 17 months.

The majority of ANCA-positive cases reported in association with antithyroid drugs in the literature are women, which has been attributed to the higher levels of thyrotoxicosis in women [5]. Similarly, in our study, most of the ANCA-positive patients were women (16/24, 67%).

In our study, 34 of 45 patients in the on-treatment group (34/45, 75%) and 20 of 33 patients in the untreated group (20/33, 60%) had Graves' disease. However, comparison of p-ANCA frequency in patients with Graves' disease in the two groups did not result in a statistically significant difference ($P = 0.38$). Our findings suggested that not only antithyroid drug treatment, but also the autoimmune nature of the disease contributes to ANCA positivity in patients with Graves' disease.

There is limited data in the literature regarding the frequency of p-ANCA positivity in Graves' disease patients. One of the most comprehensive studies on this topic is the trial in which 407 patients with Graves' disease, 200 patients with Hashimoto's thyroiditis, and 649 individuals with normal thyroid functions were investigated [29]. In that study, ANCA positivity was reported as being 19.9%

in patients with Graves' disease, 8% in those with Hashimoto's thyroiditis, and 4.6% in the euthyroid group; a significantly increased frequency was noted in the group of patients with Graves' disease when compared to the control group, while the difference between the control group and the group of patients with Hashimoto's thyroiditis was not statistically significant. The same study also reported a significantly higher rate of ANCA positivity for patients under PTU treatment when compared to those receiving carbimazole. Another study investigating ANCA frequency with IFA in autoimmune thyroid diseases reported ANCA positivity in 28.5% of patients with Graves' disease and in 9% of those with Hashimoto's disease [32].

Although no significant difference was detected in overall ANCA positivity between the two groups in our study ($P = 0.13$), p-ANCA and mpo-ANCA positivity had a significantly higher frequency in the on-treatment group ($P = 0.04$ and $P = 0.01$, respectively). Our study also demonstrated that the anti-thyroid drugs do not significantly increase the ANCA frequency according to untreated group in Graves' disease. This may indicate that, in autoimmune thyroid disease (Graves' disease), where higher frequencies of autoantibody (ANCA) than normal levels are observed, antithyroid drugs do not significantly alter this ratio. On the other hand, we determined a significant increase in the p-ANCA frequency in the on-treatment group when the two groups were compared in terms of non-autoimmune thyroid diseases (multinodular goiter and toxic adenoma). This was a remarkable finding from our study, given the data reported in the literature indicating higher ANCA positivity in autoimmune thyroid diseases.

The most common ANCA sub-type reported in the literature in association with antithyroid drugs is p-ANCA [30]. However, the most frequently detected p-ANCA subgroup is mpo-ANCA [5, 23, 27, 33]. Previous studies have reported mpo-ANCA frequencies ranging from 0 to 6.7% in patients with Graves' disease who received no previous treatment [27, 33, 34]. No mpo-ANCA positivity was noted in the untreated group in this study, while mpo-ANCA positivity was detected in 7 of the p-ANCA positive patients in the on-treatment group (7/24, 29%). Somewhat lower compared to the results of some previous studies, this finding indicates that other target antigens of p-ANCA (lactoferrin, elastase, cathepsin G, alpha enolase, β-glucuronidase, BPI, lysozyme) are also influential in drug-associated ANCA positivity, perhaps to the same extent as mpo-ANCA. In a study investigating ANCA frequency in patients with Graves' disease treated with MMI, Gumà et al. [3] reported that BPI-ANCA was the most frequently detected subgroup of p-ANCA before and after MMI treatment. It was not possible to arrive at a conclusion regarding this finding since other subgroup target antigens of p-ANCA were not assessed in this study.

Previous studies have reported various frequencies of mpo-ANCA in patients treated with PTU, ranging from 4.1 to 64% [23, 27, 33, 34]. This study determined the mpo-ANCA frequency as 29% in the on-treatment group, consistent with previous reports.

In our study, p-ANCA was positive in 21 of 41 patients receiving PTU (21/41, 51%), whereas p-ANCA positivity was noted in 3 of 4 patients treated with MMI (3/4, 75%). Most of the previously published studies have reported significantly lower frequencies of mpo-ANCA in patients treated with MMI when compared to those treated with PTU. p-ANCA was positive in 3 out of 4 patients receiving MMI, and one of these 3 subjects was also mpo-ANCA positive. A statistically significant difference was not noted between patients treated with PTU and MMI ($P = 0.6$). We are of the opinion that this finding may not be generalized since the number of subjects was very limited in the group receiving MMI.

High ANCA titers have been observed in patients' serum samples obtained before treatment in studies with Graves' disease patients, which has been associated with the nature of the disease [3, 32, 34]. Other studies have reported marked decreases in ANCA levels with MMI treatment. Another study has described significant reductions with MMI treatment in ANCA levels, for which high levels were measured before treatment [3]. A further study reported ANCA frequencies of 22% in the group receiving PTU and 2.9% in the non-treated group, while ANCA was negative in all patients treated with MMI [35]. It was therefore suggested that MMI should be considered as the first choice of treatment if long-term antithyroid treatment is necessary, given the higher frequencies of ANCA positivity with PTU treatment [3, 5, 7, 22, 27].

In our study, treatment with PTU caused markedly more ANCA positivity in our subjects. Given the ANCA positivity, ANCA-positive vasculitis and hepatotoxicity [36] risks with PTU treatment, we believe that MMI treatment should be particularly preferred in patients diagnosed with hyperthyroidism, excluding cases of hyperthyroidism crisis and thyroid storm.

c-ANCA was positive in 3 of 33 untreated subjects in our study, whereas no c-ANCA positivity was observed among 45 on-treatment patients. Besides, mpo-ANCA positivity was not detected in untreated patients while it was significantly higher in the on-treatment group. Consistent with those reported by previous studies, these results indicate that antithyroid drugs are more associated with p-ANCA and mpo-ANCA positivity.

It should be borne in mind that ANCA positivity (and associated ANCA-positive vasculitis, though rare) may present significant difficulties for us in our daily medical practices. As demonstrated in our study, high ANCA frequencies are observed in hyperthyroidism, independent

of PTU treatment. This frequency, however, increases significantly in patients with hyperthyroidism receiving antithyroid treatment (particularly with PTU), specifically in p-ANCA and mpo-ANCA subgroups. Therefore, MMI treatment should be preferred if antithyroid drugs are to be used as the treatment for hyperthyroidism (excluding rare cases of hyperthyroidism crisis and thyroid storm). Patients should be evaluated for ANCA positivity in the event that signs and/or evidence suggesting drug adverse effects. Medical treatment should be reviewed for ANCA-positive patients and definitive treatment should be considered.

Acknowledgment This study was supported by the Research Projects Fund Unit of Istanbul University, Grant No. 1860, 2008.

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