Increased Prevalence of Thyroid Disease in Patients with Antineutrophil Cytoplasmic Antibodies–associated Vasculitis

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ABSTRACT. ***Objective.*** Antineutrophil cytoplasmic antibodies (ANCA)–associated vasculitis (AAV) has been linked with thyroid disease as a result of antithyroid medications. We assessed the prevalence of thyroid disease in our patients with AAV.

Methods. Clinical records of 279 patients with AAV diagnosed between 1991 and 2014 were analyzed.

Results. Thyroid disease was identified in 21.5% of patients, but only 2 had previously received propylthiouracil. There was a greater proportion of female patients, patients with antimyeloperoxidase antibodies, and patients with renal disease in the group with thyroid disease.

Conclusion. Our data show a higher prevalence of thyroid disease in patients with AAV than the general population. This was not attributable to antithyroid drugs. (J Rheumatol First Release March 15 2018; doi:10.3899/jrheum.170661)

Key Indexing Terms:
ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES
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The etiology of autoimmune disease remains to be fully understood, and there are often interactions between genetic and environmental factors. There is a known association between different autoimmune diseases, both organ-specific and systemic[1]. Autoimmune thyroid disease is documented to be associated with other organ-specific autoimmune diseases such as type 1 diabetes, Addison disease, and celiac disease, and has also been associated with systemic autoimmune diseases such as systemic lupus erythematosus and Sjögren syndrome[2,3,4]. Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) has been reported to be associated with other systemic autoimmune diseases such as antiglomerular basement membrane disease, rheumatoid arthritis, and systemic sclerosis[5,6,7,8]. There have been small case series and a case-control study associating thyroid disease and AAV[9,10]. Some of these associate the induction of ANCA with antithyroid agents such as propylthiouracil (PTU) or carbimazole. However, other studies have shown either a low incidence of development of ANCA despite continued use of PTU, or absence of vasculitic symptoms despite the development of ANCA[11,12,13]. In our clinical practice, we noted a higher prevalence of thyroid disease than would be expected in the general population and it was seemingly unrelated to antithyroid drugs. We therefore performed a retrospective analysis of patients with AAV in our center to identify the prevalence of thyroid disease and its association with the use of antithyroid drugs.

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MATERIALS AND METHODS

We identified all patients with a diagnosis of AAV from a clinical database of patients seen in our unit between 1991 and 2014. Patients were included regardless of different organ involvement; not all patients had evidence of renal involvement. Patients were excluded if they were diagnosed prior to 1990 or if insufficient clinical information was available. A retrospective analysis of patient notes and laboratory data was carried out and data were collected on age, sex, ethnicity, ANCA specificity, organ involvement, and evidence of renal impairment. We identified the presence of thyroid disease and use of antithyroid drugs.

Because this was a retrospective study and all treatment decisions were made prior to our assessment, research ethics approval was not required for this report, in accordance with the UK National Health Service Research Ethics Committee guidelines.

Statistics. Mann-Whitney U test was used for continuous variables and chi-square test for the difference in proportions between 2 groups. Logistic regression was used for multivariate analysis and results are expressed as OR with 95% CI. Results are reported as statistically significant when $p < 0.05$.

RESULTS

Of the 325 patients with vasculitis who were managed in our unit since 1991, 46 of these were excluded because of insufficient information. Of 279 patients with AAV, 60 (21.5%) had evidence of thyroid disease: 49 (17.6%) patients had hypothyroidism (5 patients with transient or subclinical hypothyroidism), 10 had hyperthyroidism (5 patients had transient or subclinical hyperthyroidism), and 1 patient had goiter without derangement of thyroid function. Of the

patients with hyperthyroidism, 3 developed subsequent hypothyroidism after antithyroid treatment. Two of the patients with derangement of thyroid function also had goiter and 2 had thyroid nodules. There were 43 (71.7%) patients who received treatment with thyroxine, 3 patients (5%) who received radioiodine followed by thyroxine, and only 2 patients (3.3%) who were treated with PTU.

The group of patients with AAV and thyroid disease was compared to those with AAV and no thyroid disease (Table 1). The patients with thyroid disease were more likely to be women than those without (73.3% vs 45.2%, p = 0.0002) and patients of Indo-Asian origin were also more likely to have thyroid disease than not (26.7% vs 14.2%, p = 0.02). A greater proportion of the patients with thyroid disease were found to have evidence of renal disease (95.0% vs 81.7%, p = 0.02) as part of their vasculitis, and a smaller proportion had ENT involvement (25.0% vs 48.4%, p = 0.02; Figure 1). More patients with AAV and thyroid disease were antimyeloperoxidase (MPO) antibody–positive than negative for MPO-ANCA (58.3% vs 34.7%, p = 0.0016). In multivariate analysis, OR of patients with thyroid disease having MPO-ANCA specificity was 2.0 (p = 0.025), of being female was 3.3 (p = 0.0004), and of having renal organ involvement was 4.5 (p = 0.018; Table 2).

DISCUSSION

In our cohort of 279 patients with AAV, the overall prevalence of thyroid disease was 21.5%. The prevalence of hypothyroidism was 17.6%; this is much higher than the reported population prevalence of hypothyroidism in the United Kingdom, which is around 1%. This was particularly evident in women for whom the prevalence of hypothyroidism in our cohort was 30.8% compared to around 2% in the general population[14]. The prevalence of hyperthyroidism was also higher but the difference less marked, with 3.6% in our population compared to a reported population prevalence of 0.5–2.0%[14]. This was seemingly independent of the use of antithyroid drugs, with only 2 documented cases of previous PTU use in our series. This is similar to a previously reported prevalence of thyroid disease of 20% in 158 patients with AAV, and 38% in women with AAV, in an American case-control series; they also reported a low rate of use of antithyroid drugs (2/129 patients)[9]. A Swedish study reporting comorbidities in patients with AAV found a slightly lower prevalence of thyroid disease of 14.5%; in keeping with our findings, they also reported that the increased prevalence is more striking in women, but there are no further data available regarding type of thyroid disease or treatment[15].

Table 1. Characteristics of AAV patients with and without thyroid disease. Values are % unless otherwise specified.

Characteristics	Thyroid Disease History, n = 60	No Thyroid Disease History, n = 219	p
Female	73.3	45.2	0.0002
Ethnicity			
White	65	73.1	NS
Afro-Caribbean	1.7	4.1	NS
Indo-Asian	26.7	14.2	0.02
Mixed heritage	0	3.2	NS
Unknown	6.7	6.8	NS
ANCA specificity			
MPO	56.7	30.6	0.0004
PR3	33.3	54.3	0.006
MPO and PR3	1.7	4.1	NS
Negative	8.3	11	NS
Current or ever smoker	70	73.5	NS

AAV: antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis; MPO: myeloperoxidase; PR3: proteinase 3; NS: not significant.

Patients with AAV and thyroid disease were more likely to have MPO-ANCA specificity than not. This association of MPO vasculitis and thyroid disease has also been described in 1 small case series and in the case-control study of patients with AAV in the United States (all of whom had renal disease)[9,10]. Most but not all our patients had evidence of renal involvement as part of their vasculitis, and thyroid disease seemed to correlate with the presence of renal disease; derangement of thyroid function has been associated with decreased kidney function in previous studies. The mechanisms underlying this association are unclear, although altered iodine handling in patients with low estimated glomerular filtration rate and hemodynamic changes in patients with thyroid disease have been suggested[16,17]. Thyroid disease also seemed to be less common in patients with ENT disease, although this is likely because of the inverse correlation of ENT disease with MPO-ANCA specificity. There were 58.3% of patients with proteinase-3 (PR3)–ANCA who had documented ENT disease, while only 20.7% of those had MPO-ANCA. There was no difference in vasculitis outcomes between the patients with and without thyroid disease. Mortality rate and proportion of patients with stage 5 chronic kidney disease 5 at final followup were not significantly different between the 2 groups, although detailed information on clinical outcomes was not collected.

Human thyroid peroxidase (TPO) antibody and MPO have 44% sequence homology, raising the possibility that cross-reactivity between TPO and MPO is responsible for the increased thyroid disease in patients with AAV. Although it has been reported that anti-TPO and anti-MPO antibodies can cross-react, this has not been proven in other studies, and it may be that antibodies can only cross-react when peptide sequences are denatured or reduced[18,19,20]. Alternatively, rather than direct cross-reactivity, general loss of tolerance to peroxidases could explain this association.

Our study has several limitations. This was a retrospective study and there may have been missing data. It was difficult to ascertain the temporal relationship between diagnosis of thyroid disease and diagnosis of AAV. Although in some

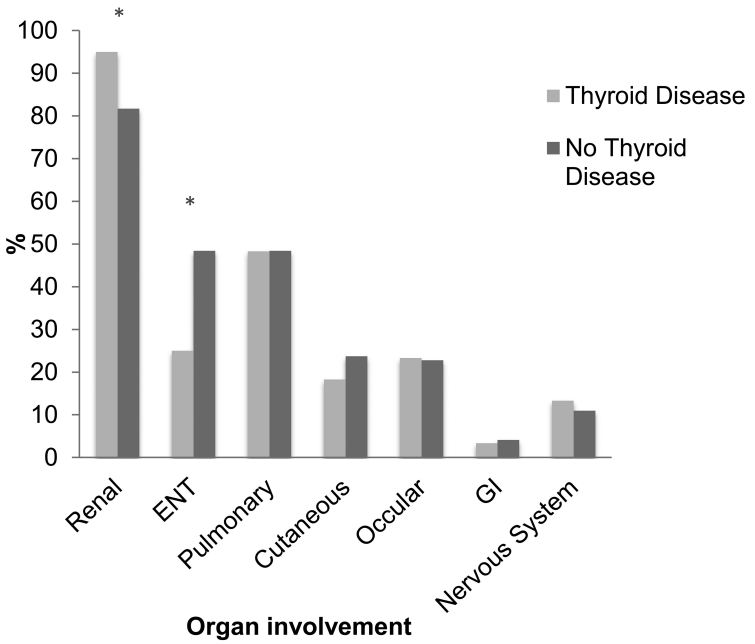

Figure 1. Organ involvement of vasculitis in patients with AAV, with and without thyroid disease. *p < 0.05. AAV: antineutrophil cytoplasmic antibody–associated vasculitis; GI: gastrointestinal.

Table 2. Multivariate association of thyroid disease among patients with AAV. Values are n (%) unless otherwise specified.

Variables	Thyroid Disease, n = 60	No Thyroid Disease, n = 219	OR (95% CI)	p
Female	44 (73.3)	99 (45.2)	3.3 (1.7–6.3)	0.0004
Renal disease	57 (95)	179 (81.7)	4.5 (1.3–15.4)	0.018
MPO-ANCA specificity	35 (58.3)	76 (34.7)	2.0 (1.1–3.8)	0.025
Indo-Asian ethnicity	16 (26.7)	31 (14.2)	1.5 (0.7–3.2)	0.246

AAV: antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis; MPO: myeloperoxidase.

patients it was clear that their hypothyroidism was secondary to treated or burned-out hyperthyroidism, it was not possible to be certain of the etiology of hypothyroidism in others. Another limitation is that information regarding the presence of TPO antibodies was extremely limited. Of the patients with thyroid disease and AAV, 20 (33.3%) had anti-TPO antibodies measured, with 6 patients having positive antibody titers; 3 of these patients had MPO-ANCA and 3 had PR3-ANCA. It is possible that some of our patients with negative anti-TPO antibodies had previously positive titers, although a study by Westman, *et al* suggested that thyroid antibodies persist over time despite patients being immunosuppressed and becoming ANCA-negative, suggesting that the 14 patients with negative thyroid antibodies may have been so throughout[21]. Despite its limitations, our study is the largest cohort of patients with AAV reporting this association with thyroid disease and MPO-ANCA, to our knowledge.

Given the high prevalence of thyroid disease, particularly hypothyroidism, in our group of patients with AAV, we would suggest that patients diagnosed with AAV should be assessed for evidence of thyroid disease or antithyroid antibodies through periodic testing of thyroid function.

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REFERENCES

1. Szyper-Kravitz M, Marai I, Shoenfeld Y. Coexistence of thyroid autoimmunity with other autoimmune diseases: friend or foe? Additional aspects on the mosaic of autoimmunity. Autoimmunity 2005;38:247-55.
2. Biró E, Szekanecz Z, Czirják L, Danko K, Kiss E, Szabó NA, et al. Association of systemic and thyroid autoimmune diseases. Clin Rheumatol 2006;25:240-5.

3. Pyne D, Isenberg DA. Autoimmune thyroid disease in systemic lupus erythematosus. Ann Rheum Dis 2002;61:70-2.
4. Perez B, Kraus A, Lopez G, Cifuentes M, Alarcon-Segovia D. Autoimmune thyroid disease in primary Sjogren's syndrome. Am J Med 1995;99:480-4.
5. Draibe J, Salama AD. Association of ANCA associated vasculitis and rheumatoid arthritis: a lesser recognized overlap syndrome. Springerplus 2015;4:50.
6. Douglas G, Bird K, Flume P, Silver R, Bolster M. Wegener's granulomatosis in patients with rheumatoid arthritis. J Rheumatol 2003;30:2064-9.
7. Derrett-Smith EC, Nihtyanova SI, Harvey J, Salama AD, Denton CP. Revisiting ANCA-associated vasculitis in systemic sclerosis: clinical, serological and immunogenetic factors. Rheumatology 2013;52:1824-31.
8. Levy JB, Hammad T, Coulthart A, Dougan T, Pusey CD. Clinical features and outcome of patients with both ANCA and anti-GBM antibodies. Kidney Int 2004;66:1535-40.
9. Lionaki S, Hogan SL, Falk RJ, Joy MS, Chin H, Jennette CE, et al. Association between thyroid disease and its treatment with ANCA small-vessel vasculitis: a case-control study. Nephrol Dial Transplant 2007;22:3508-15.
10. Tanaka A, Maeda K, Sawai K, Okuda J, Sugawara A, Kuwahara T. Concealed hypothyroidism in patients with myeloperoxidase antineutrophili cytoplasmic autoantibodies- (MPO-ANCA) positive renal disease. Clinical Nephrol 1999;52:91-5.
11. Harper L, Chin L, Daykin J, Allahabadia A, Heward J, Gough SC, et al. Propylthiouracil and carbimazole associated-antineutrophil cytoplasmic antibodies (ANCA) in patients with Graves' disease. Clin Endocrinol 2004;60:671-5.
12. Noh JY, Asari T, Hamada N, Makino F, Ishikawa N, Abe Y, et al. Frequency of appearance of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) in Graves' disease patients treated with propylthiouracil and the relationship between MPO-ANCA and clinical manifestations. Clin Endocrinol 2001;54:651-4.
13. Ishii R, Imaizumi M, Ide A, Sera N, Ueki I, Horie I, et al. A long-term follow-up of serum myeloperoxidase antineutrophil cytoplasmic antibodies (MPO-ANCA) in patients with Graves disease treated with propylthiouracil. Endocr J 2010;57:73-9.
14. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull 2011;99:39-51.
15. Englund M, Merkel PA, Tomasson G, Segelmark M, Mohammad AJ. Comorbidities in patients with antineutrophil cytoplasmic antibody-associated vasculitis versus the general population. J Rheumatol 2016;43:1553-8.
16. Schultheiss UT, Daya N, Grams ME, Seufert J, Steffes M, Coresh J, et al. Thyroid function, reduced kidney function and incident chronic kidney disease in a community-based population: the Atherosclerosis Risk in Communities study. Nephrol Dial Transplant 2017;32:1874-81.
17. Lo JC, Chertow GM, Go AS, Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Int 2005;67:1047-52.
18. Haapala AM, Hyoty H, Parkkonen P, Mustonen J, Soppi E. Antibody reactivity against thyroid peroxidase and myeloperoxidase in autoimmune thyroiditis and systemic vasculitis. Scand J Immunol 1997;46:78-85.
19. Banga JP, Tomlinson RW, Doble N, Odell E, McGregor AM. Thyroid microsomal/thyroid peroxidase autoantibodies show discrete patterns of cross-reactivity to myeloperoxidase, lactoperoxidase and horseradish peroxidase. Immunology 1989;67:197-204.
20. Freire BA, Paula ID, Paula F, Kallenberg CG, Limburg PC, Queluz TT. Absence of cross-reactivity to myeloperoxidase of anti-thyroid microsomal antibodies in patients with autoimmune thyroid diseases. Am J Med Sci 2001;321:109-12.
21. Westman KW, Bygren PG, Ericsson UB, Hoier-Madsen M, Wieslander J, Erfurth EM. Persistent high prevalence of thyroid antibodies after immunosuppressive therapy in subjects with glomerulonephritis. A prospective three-year follow-up study. Am J Nephrol 1998;18:274-9.