Increased prevalence of thyroid disease in patients with ANCA associated vasculitis

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Abstract word count: 100 words

Manuscript word count: 1325 words

Key Words: ANCA, auto-immune disease, auto-antibodies, vasculitis, myeloperoxidase, thyroid disease, thyroid peroxidase, microscopic polyangiitis, granulomatosis with polyangiitis, anti-thyroid drugs

Running header: Thyroid disease in patients with ANCA vasculitis

Abstract

Objectives: ANCA associated vasculitis (AAV) has been associated with thyroid disease due to anti-thyroid medications. We assessed the prevalence of thyroid disease in our patients with AAV.

Methods: Clinical records of 279 AAV patients diagnosed between 1990 and 2016 were analysed.

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

Conclusions: Our data shows a higher prevalence of thyroid disease in patients with AAV than the general population. This was not attributed to anti-thyroid drugs.

Introduction

The aetiology of autoimmune disease remains incompletely understood, and there are often interactions between genetic and environmental factors. It is known that there is an 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's disease and Coeliac disease, and has also been associated with systemic autoimmune diseases such as systemic lupus erythematosus (SLE) and Sjogren's syndrome.(2) (3, 4) anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) has been reported to be associated with other systemic autoimmune diseases such as anti-GBM disease, rheumatoid arthritis and systemic sclerosis. (5-8) There have been small case series and a case control study associating thyroid disease and AAV.(9, 10) Some of these implicate induction of ANCA by anti-thyroid 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.(11-13) In our clinical practice we noted a higher prevalence of thyroid disease than would be expected in the general population and seemingly unrelated to anti-thyroid drugs. We therefore performed a retrospective analysis of patients with AAV in our centre to identify the prevalence of thyroid disease and its association with the use of anti-thyroid drugs.

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 and 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, gender, ethnicity, ANCA specificity, organ involvement and evidence of renal impairment. We identified the presence of thyroid disease and use of anti-thyroid drugs.

As 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 χ^2 test for the difference in proportions between two groups. Logistic regression was used for multivariate analysis and results are expressed as odds ratio (OR) with 95% confidence interval. Results are reported as statistically significant when $p<0.05$

Results

325 patients with vasculitis were managed in our unit since 1990 and 46 of these were excluded due to 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 (3.6%) had hyperthyroidism (5 patients with transient or subclinical hyperthyroidism) and 1 patient had goitre without derangement of thyroid function. Of the patients with hyperthyroidism, 3 developed subsequent hypothyroidism after anti-thyroid treatment. Two of the patients with derangement of thyroid function also had goitre and 2 had thyroid nodules. Forty-three patients (71.7%) received treatment with thyroxine, 3 patients (5%) received radio-iodine followed by thyroxine, and only 2 patients (3.3%) were treated with propylthiouracil.

The group of patients with AAV and thyroid disease were compared to those with AAV and no thyroid disease (Table 1). The patients with thyroid disease were more likely to be female than those without (73.3% vs. 45.2%, p=0.0002) and more likely to be of Indo-Asian origin than other ethnicities (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% 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) (Table 1). More patients with AAV and

thyroid disease were anti-myeloperoxidase (MPO) antibody positive than negative for MPO ANCA (58.3% vs. 34.7%, p=0.0016). On multivariate analysis, the odds ratio of patients with thyroid disease having MPO ANCA specificity was 2.0 (p=0.025), of being female was 3.3 (p=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 hypothroididsm in the UK 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- 3.6% in our population compared to reported population prevalence between 0.5-2.0 %.(14) This was seemingly independent of the use of anti-thyroid drugs, with only 2 documented cases of previous use of PTU 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 anti-thyroid 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 report that the increased prevalence is more striking in women, but there are no further data available regarding type of thyroid disease or treatment.(15)

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 one 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 of 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 eGFR and haemodynamic 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 to be due to inverse co-correlation of ENT disease with MPO ANCA specificity; 58.3% of patients with proteinase-3 (PR3) ANCA had documented ENT disease and only 20.7% of those with MPO ANCA. There was no difference in vasculitis outcomes between the patients with and without thyroid disease. Mortality rate and proportion of patients with CKD stage 5 at final follow up were not significantly different between the two groups although detailed information on clinical outcomes was not collected.

Human thyroid peroxidase (TPO) 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.(18-20) 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 patients it was clear that their hypothyroidism was secondary to treated or burnt out hyperthyroidism, it was not possible to be certain of the aetiology of hypothyroidism in others. Another limitation is that information regarding the presence of thyroid peroxidase 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 titres; 3 of these patients had MPO ANCA and 3 PR3 ANCA. It is possible that some of our patients with negative anti-TPO antibodies had previously positive titres, 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 AAV patients reporting this association with thyroid disease and MPO-ANCA.

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 anti-thyroid antibodies with periodic testing of thyroid function thereafter.

Acknowledgments

We acknowledge support from the NIHR Imperial Biomedical Research Centre.

Transparency Declarations

We have no conflicts of interest to declare.

Figure Legends

Table 1. Characteristics of patients with AAV with and without thyroid disease.

Table 2. Multivariate association of thyroid disease within patients with AAV

Figure 1. Organ involvement of vasculitis in patients with AAV, with and without thyroid disease. *=$p<0.05$

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