Thyroid Dysfunction in Patients with Antineutrophil Cytoplasmic Antibody–associated Vasculitis: A Monocentric Retrospective Study

To the Editor:

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by necrotizing vasculitis in small-sized vessels such as arterioles, capillaries, and venules[1]. The possibility of a link between thyroid dysfunction and autoimmunity has been considered and its prevalence was reported differently according to each autoimmune disease[2]. Given that AAV is one of the systemic autoimmune diseases affecting most major organs[3], and there is cross-reactivity between thyroid peroxidase and myeloperoxidase (MPO) molecules[4], the prevalence of thyroid dysfunction, including autoimmune thyroiditis, may be increased in patients with AAV. Previous studies reported the higher prevalence of thyroid dysfunction in patients with AAV than in the general population[5,6,7]. However, there was no study on the prevalence of thyroid dysfunction in AAV patients in Korea. In this study, we investigate the prevalence of thyroid dysfunction and searched for

Table 1. Comparison of variables between patients with and without thyroid dysfunction.

Variables	Patients without Thyroid Dysfunction, n = 159	Patients with Thyroid Dysfunction, n = 27	p
Demographics			
Age at diagnosis, yrs	55.7 ± 14.9	57.9 ± 1.8	0.464
Male sex	51 (32.1)	6 (22.2)	0.305
Variants of AAV			0.139
MPA	80 (50.3)	19 (70.4)	
GPA	41 (25.8)	5 (18.5)	
EGPA	38 (23.9)	3 (11.1)	
ANCA positivity at diagnosis			
MPO-ANCA (or P-ANCA)	97 (61.0)	22 (81.5)	0.040
PR3-ANCA (or C-ANCA)	26 (16.4)	4 (14.8)	0.841
MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA)	6 (3.8)	2 (7.4)	0.390
ANCA-negative	42 (26.4)	3 (11.1)	0.086
Clinical manifestations at diagnosis			
General	71 (44.7)	12 (44.4)	0.984
Cutaneous	33 (20.8)	8 (29.6)	0.304
Mucous membranes and eye	8 (5.0)	4 (14.8)	0.056
Ear, nose, and throat	65 (40.9)	6 (22.2)	0.065
Pulmonary	88 (55.3)	16 (59.3)	0.705
Cardiovascular	39 (24.5)	9 (33.3)	0.334
Gastrointestinal	10 (6.3)	0 (0)	0.180
Renal	89 (56.0)	20 (74.1)	0.077
Nervous systemic	52 (32.7)	6 (22.2)	0.277
Vasculitis activity and prognostic factors at diagnosis			
BVAS	12.5 ± 7.1	13.8 ± 6.9	0.381
2009 FFS	1.3 ± 1.0	1.6 ± 1.0	0.074
Followup duration, mos	49.4 ± 48.9	51.6 ± 47.0	0.824
Comorbidities at diagnosis and during followup			
CKD stage 3, 4, 5	36 (22.6)	17 (63.0)	< 0.001
Endstage kidney disease	26 (16.4)	2 (7.4)	0.229
Diabetes mellitus	32 (20.1)	6 (22.2)	0.803
Hypertension	64 (40.3)	16 (59.3)	0.065
Interstitial pneumonia	7 (4.4)	10 (37.0)	0.498
Ischemic heart disease	7 (4.4)	5 (18.5)	0.006
Cardiovascular or cerebrovascular accident	16 (10.1)	0 (0)	0.085
Immunosuppressive drugs during followup			
Glucocorticoids	137 (86.2)	25 (92.6)	0.357
Cyclophosphamide	64 (40.3)	14 (51.9)	0.259
Rituximab	16 (10.1)	4 (14.8)	0.461
Azathioprine	52 (32.7)	10 (37.0)	0.659
Mycophenolate mofetil	12 (7.5)	0 (0)	0.140
Tacrolimus	8 (5.0)	1 (3.7)	0.766
Methotrexate	13 (8.2)	1 (3.7)	0.415

Values are mean ± SD or n (%). ANCA: antineutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic GPA; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham Vasculitis Activity Score; FFS: 5-factor score; CKD: chronic kidney disease.

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the predictors at diagnosis of its development during followup for 3 months or greater in Korean patients with AAV.

We retrospectively reviewed the medical records of 186 patients with AAV, who were classified as having AAV at the Department of Rheumatology, Yonsei University College of Medicine, Severance Hospital, from October 2000 to July 2018. They met the 2007 European Medicines Agency algorithms and the 2012 Chapel Hill Consensus Conferences Nomenclature of Vasculitis[1,8]. All patients had well-documented medical records regarding both AAV and thyroid diseases. This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2017-0673), and patient written informed consent was waived by the approving IRB, because this was a retrospective study.

The followup duration was defined for patients with thyroid dysfunction as the period from diagnosis to development, and as the period from diagnosis to the last visit for those without thyroid dysfunction. Overt thyroid dysfunction was approved by the International Classification Diseases, 10th revision, or by medications searched through the Korean Drug Utilisation Review system. Subclinical hyperthyroidism was defined when a thyroid-stimulating hormone (TSH) level is suppressed, but a triiodothyronine (T3) level is within a normal range, whereas subclinical hypothyroidism was defined when a TSH level is enhanced but a free thyroxine (T4) level is within a normal range[9]. Differences in variables between the 2 groups were analyzed using the chi-square and Fisher's exact tests or the Mann-Whitney U test. Comparison of cumulative thyroid dysfunction–free survival between the 2 groups was analyzed by the Kaplan-Meier survival analysis. P values < 0.05 were considered statistically significant.

Twenty-seven of 186 patients (14.5%) exhibited thyroid dysfunction, and 7 of them had overt thyroid dysfunction before diagnosis of AAV (Supplementary Table 1, available from the authors on request). The overall prevalence was lower than in previous studies (20.0–21.5%), but similar to that of another previous study (14.5%)[5,6,7]. Based on the report on thyroid dysfunction in the Korean general population[10], patients with AAV exhibited the significantly increased prevalences of overt hyperthyroidism and hypothyroidism compared to the general population (5.4% vs 0.5% and 4.3% vs 0.7%, respectively). Also, patients with AAV exhibited a lower prevalence of subclinical hyperthyroidism than the general population (1.6% vs 3.0%) but not subclinical hypothyroidism (3.2% vs 3.1%).

When we divided 186 AAV patients into the 2 groups according to the presence of thyroid dysfunction, we found that patients with thyroid dysfunction had MPO-ANCA [or perinuclear (P)-ANCA] at diagnosis more frequently than those without (81.5% vs 61.0%). During followup, chronic kidney disease (stages 3–5) and ischemic heart disease were observed in patients with thyroid dysfunction more commonly than in those without, which could suggest that thyroid dysfunction might influence the development of chronic kidney disease or ischemic heart disease. Immunosuppressive drugs were evenly administered to both groups (Table 1).

In the analysis of the development of thyroid dysfunction after AAV diagnosis, we divided 179 AAV patients into 2 groups according to each variable at diagnosis and searched for the predictors. Patients with MPO-ANCA (or P-ANCA) and the 2009 5-factor score ≥ 2 at diagnosis exhibited the lower cumulative thyroid dysfunction–free survival than those without during followup (Figure 1). Age ≥ 65 years, ANCA positivity, and renal involvement at diagnosis, but not sex, were also predictors of thyroid dysfunction (Supplementary Figure 1, available from the authors on request). It was reported that propylthiouracil (PTU) could induce AAV development, particularly in women with renal involvement[6]. In this study, because only 1 patient received PTU 8 months before AAV diagnosis, we could not clarify it.

Our study has several limitations of retrospective and monocentric study designs. The number of patients was not large enough to represent all Korean patients with AAV and no requalified results were available in all patients. However, this study is a pilot study to first discover the prevalence and the predictors at diagnosis of thyroid dysfunction in Korean patients with AAV. In the future, prospective studies with a larger number of patients and the serial results of thyroid function test will provide more reliable and validated information on the clinical implication of thyroid dysfunction in patients with AAV.

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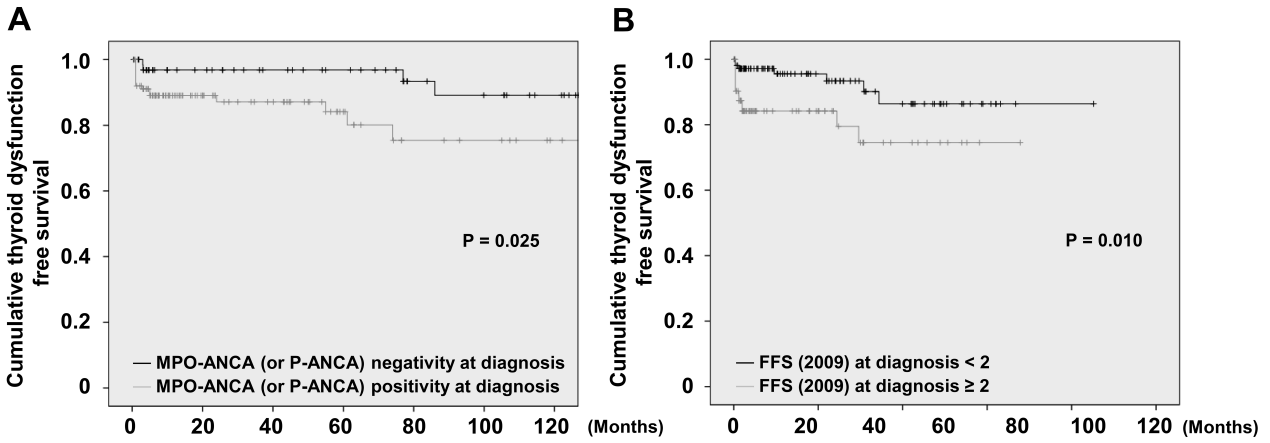

Figure 1. Predictors at diagnosis of thyroid dysfunction development. MPO-ANCA (or P-ANCA) positivity and 2009 FFS ≥ 2 at diagnosis were the predictors of the development of thyroid dysfunction after diagnosis. MPO: myeloperoxidase; ANCA: antineutrophil cytoplasmic antibody; P: perinuclear; FFS: 5-factor score.

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