The Burden of Fatigue is Associated with High TSH/fT4 ratio in Koreans with Primary Sjogren syndrome

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Background/Aims: To investigate the prevalence of anti-thyroid autoantibodies, abnormal thyroid function, and their clinical impacts in Korean patients with primary Sjögren's syndrome (pSS)

Methods: One hundred ninety six pSS patients, satisfying ACR/EULAR criteria, were enrolled. Those with overt thyroid disease (n=22) or thyroid cancer (n=4) were excluded. Clinical variables including EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and Patient Reported Index (ESSPRI) were collected. For the relative contribution of fatigue to ESSPRI, the fraction of fatigue (Ffatigue) was calculated using ESSPRI fatigue/ESSPRI score. Laboratory data including the complete blood count, ESR, and levels of thyroid-stimulating hormone, free T4, IgG, β2-microglobulin, cryoglobulin, and complement C3 and C4 were assessed. TSH/fT4 ratio was calculated. Anti-thyroglobulin (TG), anti-thyroperoxidase (TPO), TSH-binding inhibiting immunoglobulin(TBII), and anti-TSH receptor antibody(TSHR) were measured. Subclinical hypothyroidism(ST) was defined as TSH >4.0 and the presence of hypothyroidism-related autoantibodies. The Mann-Whitney test, Chi-squared or Fischer's exact test, and logistic regression analysis were performed.

Results: Of 196 patients, 71 (36.2%) had one of the anti-thyroid autoantibodies(ab) and 53 had one of the hypothyroidism-related ab. The prevalence of anti-TG, anti-TPO, TBII, and anti-TSHR was 31 (15.8%), 28 (14.3%), 8 (4.1%), and 28 (14.3%). Patients aged over 60 years old showed a higher positivity of anti-TPO which is related to TSH >4.0 or TSH/fT4 ratio>=4.14. Patients with anti-TSHR positive showed higher prevalence of ESSDAI>5.0, lung and PNS involvement and higher ESR and IgG level. Stratified by thyroid function status, patients in the higher Ffatigue were prevalent in subclinical hypothyroidism and presented more with ESSDAI joint domain. In predicting F fatigue, TSH/fT4>= 4.14 turned out to be the only significant predictor while thyroid function status was not.

Conclusions: TSH/fT4 ratio with a cutoff value of 4.14 was significantly associated with fatigue-dominance of ESSPRI, which may be applied to assess the neuroendocrine aspects of pSS.
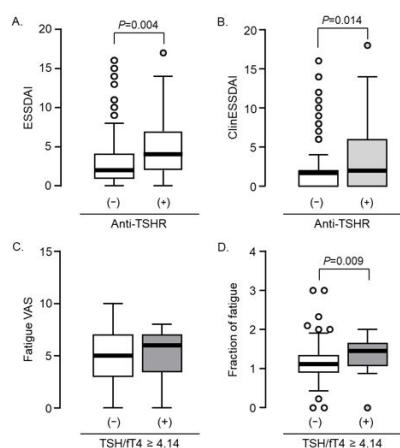
Figure 1. ESSDAI (A) and clinical ESSDAI (ClinESSDAI, B) levels were significantly different according to anti-TSH receptor (TSHR) positivity. Fatigue VAS levels were compatible (C) but fractions of fatigue in ESSPRI were significantly higher in patient with TSH/fT4 ≥4.14 (D) than those with TSH/fT4 <4.14. P values were calculated by the Mann-Whitney test.

Table 1. Logistic regression analysis with the highest quartiles of F~fatigue~ as a dependent variable.

Variables with p <0.1 in univariate analyses were incorporated into the multivariate analysis.

| Variables | Univariate | | Multivariate | | | |
| | | | Model 1 | | Model 2 | |
	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P
Age	0.968 [0.945-0.992]	0.010	0.964 [0.939-0.988]	0.004	0.961 [0.937-0.986]	0.003
Age at diagnosis	0.968 [0.944-0.993]	0.013	-	-	-	-
TSH/fT4	1.234 [0.999-1.523]	0.051	1.301 [1.049-1.662]	0.017	-	-
TSH/fT4 ≥4.14	5.601 [2.036-15.408]	0.001	-	-	7.226 [2.510-20.800]	2.460E-4
Subclinical hypothyroidism	2.558 [1.043-6.272]	0.040	-	-	-	-
ALC	0.999 [0.999-1.000]	0.028	-	-	-	-