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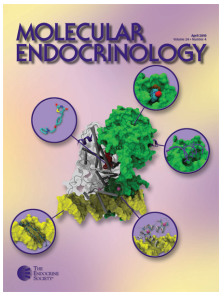

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Prevalence of Thyroid Autoimmunity in Sporadic Idiopathic Hypoparathyroidism in Comparison to Type 1 Diabetes and Premature Ovarian Failure

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Context: Thyroid autoimmunity is the most common coexistent endocrinopathy in type 1 diabetes (T1D), Addison's disease, and premature ovarian failure (POF). Although the role of autoimmunity is being investigated in patients with sporadic idiopathic hypoparathyroidism (SIH), there is little information on coexistent thyroid autoimmunity.

Objective: Our objective was to assess the prevalence of thyroid peroxidase autoantibodies (TPOAb) and thyroid dysfunction in patients with SIH and its comparison with that in T1D, POF, and Hashimoto's thyroiditis (HT) and age- and sex-matched healthy controls (for SIH).

Design and Setting: We conducted a case control study in a tertiary care setting.

Patients and Methods: Subjects were consecutive patients with SIH (n = 87), T1D (n = 100), POF (n = 58), and HT (n = 47) and healthy controls (100 females and 64 males). Serum free T_3, free T_4, TSH, and TPOAb (normal ≤ 34 IU/ml) were measured by electrochemiluminescence assay. Subjects with 1) serum TSH at least 5 μU/ml along with TPOAb more than 34 IU/ml; 2) TSH at least 10 μU/ml but normal TPOAb titers; or 3) Graves' disease were considered to have thyroid dysfunction.

Results: TPOAb positivity (>34 IU/ml) in females was 14.6% in SIH, 24.1% in POF, and 42.1% in T1D compared with 76.6% in HT and 9% in healthy controls. The frequencies of TPOAb positivity and thyroid dysfunction in patients with SIH were comparable to those in control and POF groups, but significantly less than in T1D and HT groups.

Conclusion: The frequencies of TPOAb and thyroid dysfunction were not significantly higher in patients with SIH than in healthy controls, unlike in patients with T1D and POF. (***J Clin Endocrinol Metab* 91: 4256–4259, 2006**)

THYROID AUTOIMMUNITY is the most common coexistent endocrinopathy in several autoimmune endocrine disorders including type 1 diabetes (T1D), Addison's disease, and premature ovarian failure (POF) (1–5). Clustering of autoimmune endocrine disorders indicates the possibility of shared immunogenetic mechanisms and is relevant for the clinical management of these disorders (1–5).

The autoimmune basis of sporadic idiopathic hypoparathyroidism (SIH) has been under investigation since 1966 when Blizzard *et al.* (6) reported parathyroid autoantibodies in 33% of the patients. Generalized T lymphocyte activation (7) and calcium-sensing receptor autoantibodies (CASRAb) have been reported in patients with SIH (8–10). Although these observations suggest the role of autoimmune mechanisms in the pathogenesis of SIH, coexistent thyroid autoimmunity has not been investigated in these patients (1, 11). We assessed the presence of thyroid peroxidase autoantibodies (TPOAb) in patients with SIH and compared it to that observed in T1D, POF, Hashimoto's thyroiditis (HT), and age- and sex-matched healthy controls.

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Abbreviations: APECED, Autoimmune ectodermal polyendocrinopathy; BMI, body mass index; CASRAb, calcium-sensing receptor autoantibodies; GADAb, glutamic acid decarboxylase antibodies; HSD, highest significant difference; HT, Hashimoto's thyroiditis; POF, premature ovarian failure; SIH, sporadic idiopathic hypoparathyroidism; T1D, type 1 diabetes; TPOAb, thyroid peroxidase autoantibodies.

Subjects and Methods

Subjects

The study subjects were consecutive patients with SIH (n = 87), T1D (n = 100), POF (n = 58), and HT (n = 47) attending endocrine clinics of the All India Institute of Medical Sciences (AIIMS), New Delhi, and healthy controls (100 females and 64 males). Clinical characteristics of the majority of the patients included in the current study and the diagnostic criteria used have been described in detail in our previous studies (9, 12–16) and in Tables 1 and 2. Briefly, the diagnosis of SIH was based on the presence of hypocalcemia, hyperphosphatemia, and inappropriately low serum intact PTH. The serum total calcium, phosphorus, and intact PTH values (median and range) of the study group were 5.5 mg/dl (2.2–7.9), 6.4 mg/dl (4.5–11.0), and 3.9 pg/ml (undetectable, 62.0), respectively. Patients with postsurgical hypoparathyroidism were excluded. None of the patients had family history suggestive of hypoparathyroidism or clinical features of autoimmune ectodermal polyendocrinopathy (APECED) syndrome. Autoimmune adrenal involvement was excluded by demonstrating normal serum cortisol and plasma ACTH (0800 h) value and absence of adrenal cortical autoantibodies on indirect immunofluorescence (17). The sex ratio and clinical features (convulsion, 64.7%; cataract, 53.0%; and intracranial calcification, 74.2%) of the patients in the current study were similar to those described earlier (12–15). Patients with T1D were recruited from the Diabetes of Young Clinic at AIIMS and included subjects with age at onset of disease less

TABLE 1. Clinical characteristics and thyroid peroxidase positivity and thyroid dysfunction in female patients with SIH

Parameters	SIH (n = 41)	T1D (n = 57)	HT (n = 47)	POF (n = 58)	Controls (n = 100)
Mean age (yr)	30.2 ± 11.8	23.4 ± 9.9[a]	34.4 ± 13.6[b]	29.2 ± 6.6	29.0 ± 12.9[b]
Mean BMI (kg/m^2)	21.8 ± 5.1	19.3 ± 4.0[a]	22.5 ± 3.9[b]	22.0 ± 4.2[b]	23.2 ± 5.1
Duration of clinical symptoms (yr) (median, range)	4.0 (0.1–27)	9.0 (0.1–25)[a]	1.0 (0.1–19)[b]	3.0 (0.1–14)[b]	NA
Subjects with TPOAb > 34 IU/ml (n, %)	6 (14.6%)[a,b]	24 (42.1%)[c]	36 (76.6%)[d]	14 (24.1%)[b]	9 (9.0%)[a]
Odds ratio (95% CI)	1.73 (0.57–5.23)	7.35 (3.10–17.42)	33.89 (12.64–86.57)	3.22 (1.29–8.0)	NA
Subjects with TPOAb > 103 IU/ml (n, %)	5 (12.2%)[a]	20 (35.1%)[c]	31 (65.9%)[d]	11 (19.0%)[a,c]	8 (8.0%)[a]
Odds ratio (95% CI)	1.54 (0.48–5.21)	6.21 (2.51–15.35)	22.28 (8.69–57.11)	2.69 (1.01–7.14)	NA
Thyroid dysfunction					
Group i: subjects with TPOAb > 34 IU/ml and TSH ≥ 5.0 μU/ml (n, %)	3 (7.3%)[a,c]	15 (26.3%)[d]	34 (72.3%)[b]	9 (15.5%)[c,d]	4 (4%)[a]
Group ii: subjects with TSH ≥10.0 μU/ml and normal TPOAb (n, %)	1 (2.4%)	5 (8.7%)[a]	5 (10.6%)[a]	1 (1.2%)	1 (1%)[b]
Group iii: Graves' disease (n)	0	1**	0	2	0
All thyroid dysfunction (i + ii + iii)	4 (9.7%)[a,c]	20 (35.0%)[d]	39 (83.0%)[b]	12 (20.6%)[c,d]	5 (5.0%)[a]
Odds ratio (95% CI)	2.05 (0.52–8.07)	10.27 (3.59–29.37)	92.6 (28.52–300.0)	4.96 (1.64–14.90)	NA

Data in the same row with *different superscripts* are significantly different from each other (ANOVA, *post hoc* Tukey HSD test, $P < 0.05$ significant). Normal TPOAb < 34.0 IU/ml. NA, Not applicable; CI, confidence interval.

**, Patient with T1D had Graves' disease 10 yr earlier. However, she showed remission following 1-yr course of carbimazole therapy and converted to hypothyroidism during follow-up and was therefore considered in thyroid dysfunction group i.

than 30 yr and requiring insulin for glycemic control. Sixty percent of them had a history of ketosis at presentation. Diabetic patients were categorized according to the classification by the American Diabetes Association expert committee (18, 19). Patients with fibrocalculous pancreatopathy as well as those achieving glycemic control with diet and oral hypoglycemic agents were excluded. Of the T1D patients, 40.2% had glutamic acid decarboxylase 65 antibodies positivity. Two of the patients with T1D had associated celiac disease. Patients with POF were diagnosed as follows: age less than 40 yr, secondary amenorrhea more than 6 months duration, and serum FSH values more than 40 mIU/ml on two occasions 4–6 wk apart and normal karyotype (16). None of the patients with POF had clinical features of adrenal insufficiency, and 0800 h serum cortisol was normal in all of them. Patients with Turner's syndrome (45,X or 46,XX/45,X karyotype) and those with a history of pelvic surgery were excluded.

Subjects with goiter and fine-needle aspiration cytology suggestive of HT were included as positive controls for thyroid autoimmunity. Males with HT were excluded because of their limited numbers (n = 4). Healthy controls included volunteers for a task force study for the Indian Council of Medical Research to generate normative data on bone mineral density in healthy north Indian Asians (n = 94) and one first-degree relative each from the family of patients with osteomalacia recruited for vitamin D receptor polymorphisms analysis (n = 70). All the control subjects had normal serum total calcium and inorganic phosphorus. The control subjects were matched in a 1:1 ratio to patients with SIH by age (within 1 yr). Additional controls with age within 1 yr of the mean age of male and female patients with SIH were included to increase the statistical power of the study. The serum samples were drawn from the subjects after institutional ethics committee approval and written informed consent.

Definitions

TPOAb positivity. Serum TPOAb titers greater than 34 IU/ml were considered positive (Roche, GmbH, Mannheim, Germany). To assess high titer TPOAb positivity, an arbitrary cutoff of 103 IU/ml (three times above the normal) was also used.

TABLE 2. Clinical characteristics and thyroid peroxidase positivity and thyroid dysfunction in male patients with SIH

Parameters	SIH (n = 46)	T1D (n = 43)	Controls (n = 64)
Mean age (yr)	33.6 ± 14.3[b]	21.6 ± 8.8[a]	33.6 ± 17.2[b]
Mean BMI (kg/m^2)	20.6 ± 4.5[a,b]	18.6 ± 2.3[a]	22.6 ± 4.8[b]
Duration of clinical symptoms (yr) (median, range)	5.0 (0.1–35)	4.0 (0.3–22)	NA
Subjects with TPOAb > 34 IU/ml (n, %)	8 (17.4%)[a,b]	11 (25.6%)[a]	6 (9.3%)[b]
Odds ratio (95% CI)	2.04 (0.65–6.3)	3.32 (1.12–9.82)	NA
Subjects with TPOAb > 103 IU/ml (n, %)	3 (6.5%)[a,b]	7 (16.3%)[a]	2 (3.1%)[b]
Odds ratio (95% CI)	2.16 (0.35–13.49)	6.03 (1.87–30.58)	NA
Thyroid dysfunction			
Group i: subjects with TPOAb > 34 IU/ml and TSH ≥ 5.0 μU/ml (n, %)	4 (8.7%)	5 (11.6%)	2 (3.1%)
Group ii: subjects with TSH ≥ 10.0 μU/ml but normal TPOAb (n, %)	0	1 (2.3%)	0
Group iii: Graves' disease (%)	0	3 (6.9%)	0
All thyroid dysfunction (i + ii + iii)	4 (8.7%)	9 (20.8%)[a]	2 (3.1%)[b]
Odds ratio (95% CI)	2.96 (0.52–16.85)	8.21 (1.67- 40.17)	NA

Data in same row with *different superscripts* are significantly different from each other (ANOVA, *post hoc* Tukey HSD test, $P < 0.05$ significant). Normal TPOAb < 34.0 IU/ml. NA, Not applicable; CI, confidence interval.

Thyroid dysfunction. In the current study, subjects with 1) serum TSH at least 5 μU/ml along with TPOAb greater than 34 IU/ml, 2) TSH at least 10 μU/ml but normal TPOAb titers, or 3) Graves' disease were considered to have clinically relevant thyroid dysfunction.

Biochemical estimations

Serum samples for the measurement of free T_3, free T_4, TSH, and TPOAb were stored at −20 C and assayed together in multiple batches by Elecsys immunoassay kits auto analyzer (Elecsys-1010, Roche Diagnostics, Mannheim, Germany). The normal ranges for serum free T_3, free T_4, TSH, and TPOAb were 3.1–6.8 pmol/liter, 12–22 pmol/liter, 0.27–4.2 μIU/ml, and greater than 34.0 IU/ml, respectively. Inter- and intraassay coefficients of variation for these measurements were 2.2, 2.9, 8.6, and 6.3%; and 2.8, 6.6, 8.7, and 9.5%, respectively. The serum FSH (Medicorp Inc., Montreal, Quebec, Canada) and intact PTH (Diasorin, Stillwater, MN; normal range, 13–54 pg/ml) were assayed by using immunoradiometric kits. Their inter- and intraassay coefficient of variations ranged from 3.5 to 8.5% and 3.4 to 3.6%, respectively. Quantitative determination of glutamic acid decarboxylase antibodies (GADAb) was performed using ^{125}I RIA using a commercial kit (DLD Diagnostica GMBH, Adlerhorst, Hamburg, Germany). Inter- and intraassay coefficients of variation for GADAb assay were 5.1 and 2.9% (normal value < 1 U/ml).

Statistical analysis

The data are given as mean ± SD. Statistical analysis was performed with SPSS statistical software (version 10.0; SPSS Inc., Chicago, IL). The significance of differences in the mean age and body mass index (BMI; kilograms per square meter) of various groups was assessed by using an ANOVA, followed by Tukey highest significant difference (HSD) test for *post hoc* analysis if ANOVA was significant. The χ^2 test with Yates correction was used to assess the significance of differences in the frequencies of TPOAb positivity and thyroid dysfunction in different groups. P value < 0.05 was considered significant.

Results

Tables 1 and 2 show the mean age, BMI, frequencies of TPOAb positivity, and thyroid dysfunction in female and male patients within the SIH group and their comparison with other groups. The mean age and BMI of both male and female patients with SIH were comparable to those of other groups (Tables 1 and 2). However, the mean age of patients with T1D was significantly less than that of the control group.

TPOAb and thyroid dysfunction in females

The frequency of TPOAb positivity (>34 IU/ml) was 14.6% in SIH, 24.1% in POF, 42.1% in T1D, 76.6% in HT, and 9% in the healthy controls. No significant difference was observed between SIH and the control groups at any of the two cutoffs used for TPOAb positivity (34 or 103 IU/ml). However, the frequencies of TPOAb positivity with both cutoffs were significantly higher in patients with POF, T1D, and HT than in the control group.

No significant difference was observed in the frequency of thyroid dysfunction (as defined in *Subjects and Methods*) between patients with SIH and the healthy controls (Table 1). In comparison, the frequencies of thyroid dysfunction were significantly higher in POF, T1D, and HT groups compared with the healthy controls. Graves' disease was observed only in the patients with POF (n = 2) and T1D (n = 1) but not in the SIH group. Across the groups, the majority of patients with thyroid dysfunction had coexistent TPOAb (Table 1).

TPOAb and thyroid dysfunction in males

No significant difference was observed in the frequency of TPOAb positivity and thyroid dysfunction at any of the cutoffs (34 IU/ml or 103 IU/ml) between SIH and the healthy controls (Table 2). This is in contrast to significantly high TPOAb positivity and thyroid dysfunction observed in the T1D group.

The frequency of TPOAb tended to be higher in patients with T1D who had GADAb positivity compared with those with no circulating GADAb (43.6 *vs.* 27.6%; $P = 0.18$). However, there was no significant difference in the thyroid dysfunction between T1D patients with and without GADAb positivity (24.1 *vs.* 25.6%; $P = 0.94$).

Discussion

The autoimmune basis of hypoparathyroidism associated with APECED syndrome is supported by the presence of parathyroid autoantibodies (20) and CASRAb in these patients (8). However, recently Soderbergh *et al.* (21) could not observe CASRAb in any of the 90 patients with hypoparathyroidism occurring in the setting of autoimmune polyendocrine syndrome type 1. The role of autoimmune mechanisms is also being investigated in patients with SIH (9–11), and there are two reports of CASRAb positivity in these patients (9, 10). Higher prevalence of coexistent TPOAb is often used as a surrogate marker for autoimmunity. Jenkins and Weetman (1) reviewed thyroid autoimmunity in various autoimmune endocrine disorders and observed its significant association with T1D and Addison's disease. Data on POF and other endocrine disorders including SIH were not conclusive because of the scarcity of published information (1, 11). The present study fills a gap in the world survey of thyroid autoimmunity in these disorders.

The results of the current study indicate that the frequency of TPOAb positivity in male and female patients with SIH was comparable to that of healthy controls, unlike the T1D and POF groups. The only study available on prevalence of thyroid autoimmunity in idiopathic hypoparathyroidism has been by Blizzard *et al.* (6), where nine of 44 female patients with hypoparathyroidism had thyroid microsomal autoantibodies on indirect immunofluorescence test. It is difficult to compare these results with the current study because several patients studied by Blizzard had features of APECED syndrome, a different assay methodology was used, and statistical significance could not be determined in the absence of age- and sex-matched controls. In a previous study of 51 patients with SIH, we did not find a significant difference in the TPOAb positivity between the cases and the controls (9). However, the controls were not gender and age matched. In the current study we have included age- and sex-matched controls. However, with 41 female and 46 male patients with SIH and 100 female and 64 male controls, the current study would have 80% power and 95% confidence interval to exclude an odds ratio of 4.0 or higher for TPOAb positivity. A large cohort of 347 patients with SIH and 920 controls would be required to confer statistical significance and power to the 1.7 odds ratio of TPOAb positivity observed in patients with SIH. Considering these facts, the preliminary trend of lower TPOAb positivity observed in patients with

SIH in comparison to T1D and POF needs further studies involving a larger number of patients with SIH.

In comparison to SIH, patients with T1D and POF showed significantly higher prevalence of TPOAb and thyroid dysfunction. The observations of the current study indicating high prevalence of TPOAb and thyroid dysfunction in patients with T1D, especially among female subjects, are in accordance with several previous studies (5, 22), including a report from our center (18). Recently, Barker *et al.* (22) screened a large cohort of 814 patients with T1D with median age of 14.8 yr (10.7–27.1) and median duration of diabetes of 3.4 yr (0.08–10.33) and reported TPOAb and/or thyroglobulin Ab expression in 29%. Thyroid autoimmunity was more common in females and increased with longer duration of diabetes (22). In the current study, the mean age and duration of diabetes were 23.4 yr and 9.1 yr, respectively, and may account for the 42% prevalence of TPOAb in the females. The association of T1D with thyroid autoimmunity has been linked to shared immunopathogenetic mechanisms. Human leukocyte antigen alleles (DR3-DQ2) have been associated with TPOAb positivity in patients with T1D (22). Patients with T1D and GADAb have a significantly higher possibility of TPOAb positivity (22). The trend of higher TPOAb positivity in patients with T1D who were GADAb positive in comparison to those with no GADAb positivity is in accordance with the previous observation of Barker *et al.* (22).

In contrast to T1D, association between POF and thyroid autoimmunity is yet to be proven conclusively (1, 11). The largest study to date on thyroid autoimmunity in POF is by Betterle *et al.* (4). Of the 50 patients with POF, 18% had clinical evidence of autoimmune thyroid disorders, and 10% had thyroid autoantibodies (4). However, the study was not case controlled. Shah *et al.* (23) studied 37 Indian patients with POF and reported a 22% prevalence of thyroid dysfunction. The current study including the largest number of subjects with POF showed 24 and 20.6% prevalence of TPOAb positivity and thyroid dysfunction, which were significantly higher than those of controls.

Thus, the results of the present study indicate that the frequency of TPOAb and thyroid dysfunction is not significantly higher in patients with SIH than in healthy controls, unlike patients with T1D and POF. However, the limited spread of thyroid autoimmunity in patients with SIH needs further exploration by involving a larger cohort of patients with SIH using a multicentric approach in view of the rarity of the disease.

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