Elmer Press

Original Article

J Endocrinol Metab. 2016;6(2):46-51

Clinical, Endocrinological and Immunological Characteristics of Japanese Patients With Autoimmune Polyglandular Syndrome Type 3a

Sumie Moriyama[a], Reo Yoshikawa[a], Hisayuki Katsuyama[a], Hidetaka Hamasaki[a], Hiroki Adachi[a], Hidekatsu Yanai[a, b]

Abstract

Background: Autoimmune polyglandular syndrome (APS) is an autoimmune disease that involves multiple organ failure. In APS3, autoimmune thyroid disease occurs with other autoimmune diseases, but not with Addison disease. APS3a is defined as APS3 including autoimmune diabetes. The information about clinical backgrounds of APS3a is very limited. We studied to understand clinical, endocrinological and immunological characteristics of Japanese patients with APS3a.

Methods: We reviewed our previously published case reports about APS3a, and picked up patients with type 1 diabetes and autoimmune diabetes, who showed the positivity for anti-glutamic acid decarboxylase antibody (anti-GAD ab) or anti-islet antigen 2 antibody (anti-IA2 ab) or anti-thyroglobulin antibody (anti-TG ab) or anti-thyroid peroxidase antibody (anti-TPO ab) or anti-thyroid stimulating hormone receptor antibody (anti-TR ab) between January 2010 and January 2016. We collected data including age, sex, anti-GAD ab, anti-IA2 ab, HbA1c, serum fasting C-peptide immunoreactivity (CPR), urinary CPR, treatment for diabetes, anti-TPO ab, anti-TG ab, anti-TR ab, thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), findings of thyroid ultrasonography and treatment for thyroid diseases.

Results: Present study revealed a remarkable female predominance in APS3a. Among patients with autoimmune diabetes, slowly progressive insulin-dependent diabetes mellitus (SPIDDM) was the most common type of diabetes, and almost 80% of patients with APS3a showed the positivity for anti-GAD ab. Among patients with autoimmune thyroid diseases, almost 80% of patients had possible Hashimoto thyroiditis. Almost 70% of patients with APS3a showed the positivity for anti-TPO ab. Almost 20% of APS3a patients had possible Grave's disease, and 83% of patients with possible Grave's disease showed overt Grave's disease. In patients with possible Grave's disease, the positive rate of anti-TR ab was 100%.

Conclusion: We revealed clinical, endocrinological and immunological characteristics of patients with APS3a in Japan.

Keywords: Autoimmune polyglandular syndrome 3a; Insulin; Thyroid diseases; Type 1 diabetes

Introduction

Autoimmune polyglandular syndrome (APS) was defined as an autoimmune disease that involves multiple organ failure [1, 2]. APS was classified into four types, and APS types 1, 2 and 4 include autoimmune adrenalitis, Addison disease, as major components of disease [3-5]. In APS3, autoimmune thyroiditis occurs with other autoimmune diseases, but not with Addison disease [3, 4]. APS3 is further classified into 3a, 3b and 3c. APS3a, APS3b and APS3c are defined as APS3 including autoimmune diabetes, pernicious anemia, vitiligo and alopecia as major components of disease, respectively [3, 4]. Autoimmune thyroid disease is the most common (> 90%) organ-specific autoimmune disease that develops as a complication among patients with type 1 diabetes in Japan [5, 6]. Therefore, APS3a may be the most common type of APS in Japan.

Although case reports about APS3a including ours were found by the search using Pubmed [4, 7-9], the information about clinical backgrounds of APS3a is very limited. Only one article reported clinical and genetic characteristics of adult APS3, and we found one more article which reported the incidence of APS3 in children with type 1 diabetes [10, 11].

To understand clinical, endocrinological and immunological characteristics of Japanese patients with APS3a, we reviewed and summarized our previous four case reports about APS3a at first. Furthermore, we showed clinical backgrounds of 26 Japanese patients with APS3a that we accumulated, and we analyzed data of these patients to find characteristic features for APS3a in Japan.

Manuscript accepted for publication March 23, 2016

[a]Department of Internal Medicine, National Center for Global Health and Medicine Kohnodai Hospital, Chiba, Japan
[b]Corresponding Author: Hidekatsu Yanai, Department of Internal Medicine, National Center for Global Health and Medicine Kohnodai Hospital, 1-7-1 Kohnodai, Ichikawa, Chiba 272-0034, Japan.
Email: dyanai@hospk.ncgm.go.jp

doi: http://dx.doi.org/10.14740/jem348e

Table 1. Clinical, Endocrinological and Immunological Characteristics of Our Previously Reported Japanese Patients With Autoimmune Polyglandular Type 3a

Cases [Reference]	Age (years)/sex	Type of diabetes	Anti-GAD antibody	Urinary C-peptide (μg/day)	Positivity for anti-TPO or anti-TG antibody	Thyroid function	Other complication
Case 1 [4]	53/F	SPIDDM	10,000	70	(+)	Euthyroid	Symptomatic Sjogren's syndrome with anti-SSA/Ro ab (+) and anti-SSB/La ab (+); asymptomatic RA with RF (+)
Case 2 [7]	83/F	SPIDDM	3.2	9.1	(+)	Treated by levothyroxine (25 μg/day)	MRHE
Case 3 [8]	68/F	SPIDDM	34	52.9	(+)	Euthyroid	None
Case 4 [9]	84/F	SPIDDM	65.2	< 0.3	(-)	Treated by levothyroxine (50 μg/day)	Sarcoidosis, candidiasis, and liver cirrhosis due to autoimmune hepatitis

F: female; GAD: glutamic acid decarboxylase; MRHE: mineralocorticoid-responsive hyponatremia with the elderly; RA: rheumatoid arthritis; ref: reference; RF: rheumatoid factor; SPIDDM: slowly progressive insulin-dependent diabetes mellitus; TG: thyroglobulin; TPO: thyroid peroxidase. Normal ranges of anti-GAD antibody and urinary C-peptide are < 1.5 U/mL and 29.2 - 167.0 μg/day, respectively.

Materials and Methods

Review and summarization of our previously published case reports about APS3a

We reviewed four our previously published case reports about APS3a, and showed data about age, sex, type of diabetes, anti-glutamic acid decarboxylase antibody (anti-GAD ab), the positivity for anti-thyroglobulin antibody (anti-TG ab) or anti-thyroid peroxidase antibody (anti-TPO ab), thyroid function and other complication in 4 patients with APS3a.

Subjects

This study was approved by the Institutional Ethics Committee in National Center for Global Health and Medicine (NCGM-G-001947-00), and was also performed in accordance with the Declaration of Helsinki.

We picked up patients with type 1 diabetes and autoimmune diabetes, who showed positivity for anti-GAD ab or anti-islet antigen 2 antibody (anti-IA2 ab) or anti-TG ab or anti-TPO ab or anti-thyroid stimulating hormone receptor antibody (anti-TR ab) between January 2010 and January 2016.

Data collection

We collected data including age, sex, anti-GAD ab, anti-IA2 ab, HbA1c, serum fasting C-peptide immunoreactivity (CPR), urinary CPR, treatment for diabetes, anti-TPO ab, anti-TG ab, anti-TR ab, thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), findings of thyroid ultrasonography and treatment for thyroid diseases.

Definition of autoimmune thyroid diseases

Grave's disease was defined as a history of primary hyperthyroidism with positive anti-TR ab, and Hashimoto thyroiditis was defined as having diffuse goiter and/or primary hypothyroidism with positive anti-TPO ab or positive anti-TG ab [12]. However, we have previously found a significant discrepancy between endocrinological phenotype and immunological phenotype in APS3a [4]. In present study, a history of primary hyperthyroidism with positive anti-TR ab was defined as overt Grave's disease, and euthyroidism with positive anti-TR ab was defined as immunological Grave's disease. We defined overt Grave's disease and immunological Grave's disease as possible Grave's disease. Having diffuse goiter and/or primary hypothyroidism with positive anti-TPO ab or positive anti-TG ab was defined as overt Hashimoto thyroiditis, and the absence of diffuse goiter and/or primary hypothyroidism with positive anti-TPO ab or positive anti-TG ab was defined as immunological Hashimoto thyroiditis. Subclinical hypothyroidism was diagnosed when peripheral thyroid hormone levels were within normal reference laboratory range but serum TSH levels were mildly elevated [13]. We defined overt Hashimoto thyroiditis and immunological Hashimoto thyroiditis and subclinical hypothyroidism with positive anti-TPO ab or positive anti-TG ab as possible Hashimoto thyroiditis.

Results

Table 1 shows clinical, endocrinological and immunological characteristics of four our previously reported Japanese patients with ASP3a [4, 7-9]. All patients were female, and age ranged from 53 to 84 years old. Type of diabetes in all patients was slowly progressive insulin-dependent diabetes mellitus

Table 2. Clinical, Endocrinological and Immunological Data of Our 26 Patients With Autoimmune Polyglandular Type 3a

Cases	Age (years)/ sex	Type of diabetes	Anti-GAD antibody (U/mL)	Anti-IA2 antibody (U/mL)	HbA1c (%)	Serum CPR (ng/ mL)	Urinary CPR (µg/ day)	Treatment for diabetes	Anti-TPO antibody (IU/mL)	Anti-TG antibody (IU/mL)	Anti-TR antibody (IU/L)	Thyroid function, findings of thyroid ultrasonography and treatment
1	80/F	UD	13	0.9	12.1	< 0.03	< 0.5	Insulin	11	207	0.4	Euthyroidism, no treatment
2 [4]	53/F	SPIDDM	10,000	11	10.2	0.26	70	Insulin	> 600	298	0.7	Euthyroidism, no treatment
3	49/M	SPIDDM	4,140	11	5.8	1.86	UD	Insulin + OAD	454	546	11.3	Euthyroidism, no treatment
4	81/F	UD	49,000	2.9	9.8	< 0.03	1.2	Insulin	< 5	82	0.4	Euthyroidism, no swelling, and no treatment
5	72/F	AOT1D	970	8.4	10	< 0.03	1.7	Insulin	109	21	25.2	Hyperthyroidism, treated by MMI
6 [8]	68/F	SPIDDM	34	< 0.4	8.3	4.77	52.9	Insulin + OAD + GLP-1 analog	71	497	0.5	Euthyroidism, no swelling, and no treatment
7	62/F	SPIDDM	1,300	< 0.4	8.7	< 0.03	UD	Insulin	195	23	0.4	Euthyroidism, no treatment
8	71/F	SPIDDM	6.3	< 0.4	11.9	6.04	36.4	Insulin	26	17	< 1	Euthyroidism, no swelling, and no treatment
9	50/M	SPIDDM	2.4	> 0.4	8.5	4.75	UD	OAD	> 600	411	0.4	Euthyroidism, no treatment
10	80/F	SPIDDM	53	< 0.4	6.8	2.64	UD	OAD	62	11	0.6	Euthyroidism, no treatment
11	69/M	SPIDDM	36	< 0.4	6.5	3.84	UD	OAD	502	480	0.7	Euthyroidism, no treatment
12 [9]	84/F	SPIDDM	65.2	UD	5.9	< 0.03	< 0.3	Insulin	< 5	< 10	UD	Hypothyroidism, treated by levothyloxine
13 [7]	83/F	SPIDDM	3.2	< 0.4	6.3	0.84	9.1	Diet + exercise	8	< 10	UD	Hypothyroidism, treated by levothyloxine
14	47/M	NGT	2.9	< 0.4	5.6	3.0	UD	No treatment	73	488	0.4	Hypothyroidism, treated by levothyloxine
15	42/M	AOT1D	39	< 0.4	10.5	0.05	4.9	Insulin	163	23	10.2	Hyperthyroidism, treated by MMI
16	43/M	AOT1D	155	< 0.4	8.6	0.18	UD	Insulin	251	946	1	Hypothyroidism, treated by levothyloxine
17	76/F	SPIDDM	57	< 0.4	7.2	1.87	UD	OAD	> 600	12	0.4	Subclinical hypothyroidism, no treatment
18	67/M	SPIDDM	2.2	< 0.4	6.9	1.65	UD	OAD	9	182	0.4	Euthyroidism, no swelling, and no treatment
19	60/F	SPIDDM	550	< 0.4	6.6	3.41	30.9	OAD	16	76	2.6	Hyperthyroidism, treated by iodine isotope treatment
20	83/F	SPIDDM	> 2,000	< 0.4	9.6	< 0.03	< 0.9	Insulin + OAD	417	121	< 0.3	Euthyroidism, no swelling, and no treatment
21	67/F	UD	< 0.3	1	7.5	< 0.03	9.8	Insulin	20	818	< 0.3	Euthyroidism, no treatment
22	42/F	AOT1D	0.7	3.9	8.7	< 0.03	UD	Insulin	8	12	164	Hyperthyroidism, treated by MMI
23	53/F	SPIDDM	< 0.3	0.5	6.6	2.64	153	Diet + exercise	8	14	4.5	Hyperthyroidism, treated by MMI
24	53/F	UD	1.1	< 0.4	9.7	0.08	UD	Insulin	392	151	0.5	Subclinical hypothyroidism, no treatment
25	52/F	AOT1D	< 0.3	< 0.4	8.0	< 0.03	< 0.9	Insulin	188	577	0.7	Euthyroidism, no treatment
26	51/M	AOT1D	< 0.3	< 0.4	12.7	0.43	UD	Insulin	27	12	< 0.3	Euthyroidism, no treatment

No swelling indicates the absence of thyroid swelling determined by thyroid ultrasonography. AOT1D: acute onset type 1 diabetes; CPR: C-peptide immunoreactivity; F: female; GAD: glutamic acid decarboxylase; GLP-1: glucagon-like peptide-1; IA2: islet antigen 2; M: male; MMI: methylmercapto-imidazole; NGT: normal glucose tolerance; OAD: oral anti-diabetic drug; SPIDDM: slowly progressive insulin-dependent diabetes mellitus; TG: thyroglobulin; TPO: thyroid peroxidase; TR: thyroid stimulating hormone receptor; UD: undetermined. Normal ranges of anti-GAD antibody, anti-IA2 antibody, serum CPR, urinary CPR, anti-TPO antibody, anti-TG antibody and anti-TR antibody are < 1.5 U/mL, < 0.4 U/mL, 0.61 - 2.09 ng/mL, 29.2 - 167.0 µg/day, < 16 IU/mL, < 28 IU/mL and < 2.0 IU/L, respectively.

Table 3. Sex, Type of Diabetes or Glucose Intolerance, the Positivity for Diabetes-Associated Autoantibodies, Treatment for Diabetes, Kinds and Thyroid Function of Autoimmune Thyroid Diseases and the Positivity for Thyroid-Associated Autoantibodies in Patients With Autoimmune Polyglandular Type 3a in Japan

Sex (male/female)	8/18
Autoimmune diabetes	
SPIDDM	15/26 (57.7%)
Acute onset type 1 diabetes	6/26 (23.1%)
Normal glucose tolerance	1/26 (3.8%)
Anti-GAD antibody (+)	20/26 (76.9%)
Anti-IA2 antibody (+)	8/26 (30.8%)
Treatment for diabetes	
Insulin	14/26 (53.8%)
Insulin + OAD	2/26 (7.7%)
Insulin + OAD + GLP-1 analog	1/26 (3.8%)
OAD	6/26 (23.1%)
Diet + exercise	2/26 (7.7%)
No treatment	1/26 (3.8%)
Autoimmune thyroid diseases	
Possible Hashimoto thyroiditis	21/26 (80.8%)
Overt Hashimoto thyroiditis	4/26 (15.4%)
Subclinical hypothyroidism due to Hashimoto thyroiditis	2/26 (7.7%)
Immunological Hashimoto thyroiditis	15/26 (57.7%)
Anti-TPO antibody (+)	19/26 (73.1%)
Anti-TG antibody (+)	15/26 (57.7%)
Possible Graves's disease	6/26 (23.1%)
Overt Grave's disease	5/26 (19.2%)
Immunological Grave's disease	1/26 (3.8%)
Anti-TR antibody (+)	6/26 (23.1%)

GAD: glutamic acid decarboxylase; GLP-1: glucagon-like peptide-1; IA2: islet antigen 2; OAD: oral anti-diabetic drug; SPIDDM: slowly progressive insulin-dependent diabetes mellitus; TG: thyroglobulin; TPO: thyroid peroxidase; TR: thyroid stimulating hormone receptor.

(SPIDDM). Anti-GAD ab levels ranged widely from 3.2 to 10,000 U/mL. Beta-cell function was preserved in two patients and was severely disturbed in two patients. Autoimmune thyroid disease in all patients was Hashimoto thyroiditis, and two patients showed euthyroidism and two patients were treated by levothyroxine. We found Sjogren's syndrome, elevated rheumatoid factor, mineralocorticoid-responsive hyponatremia with the elderly (MRHE), sarcoidosis, candidiasis, and liver cirrhosis due to autoimmune hepatitis as complications of APS3a.

We found 26 patients with APS3a. Clinical, endocrinological and immunological data of our patients with APS3a are shown in Table 2. We summarized 26 patients' data including sex, type of diabetes or glucose intolerance, the positivity for diabetes-associated autoantibodies, treatment for diabetes, kinds and thyroid function of autoimmune thyroid diseases, and the positivity for thyroid-associated autoantibodies in patients with APS3a in Japan (Table 3).

Mean ± SD and range of age, HbA1c, and levels of anti-GAD ab, anti-IA2 ab, serum fasting CPR, urinary CPR, anti-TPO ab, anti-TG ab and anti-TR ab in patients with APS3a in Japan are shown in Table 4.

Discussion

We previously found and reported a significant discrepancy between endocrinological and clinical phenotype and immunological phenotype in a female patient with APS3a [4]. In spite of her high level of anti-TPO ab and anti-TG ab, she did not show diffuse goiter and primary hypothyroidism. Further, in spite of remarkable high level of anti-GAD ab (10,000 U/mL), her beta-cell function was preserved when she was diagnosed as having APS3a. After several months, she showed an insulin-dependent state. We also experienced a female patient showing the absence of diffuse goiter and primary

Table 4. Mean ± SD and Range of Age, HbA1c, and Levels of Anti-GAD Antibody, Anti-IA2 Antibody, Serum Fasting CPR, Urinary CPR, Anti-TPO Antibody, Anti-TG Antibody and Anti-TR Antibody in Patients With Autoimmune Polyglandular Type 3a in Japan

	Mean ± SD	Range
Age	63.0 ± 14.2	42 - 86
HbA1c	8.4 ± 2.0	5.6 - 12.7
Anti-GAD antibody (U/mL)	2,632.0 ± 9,685.0	< 0.3 - 49,000
Anti-IA2 antibody (U/mL)	1.86 ± 3.26	< 0.4 - 11.0
Serum CPR (ng/mL)	1.48 ± 1.84	< 0.03 - 3.84
Urinary CPR (μg/day)	29.9 ± 55.2	< 0.5 - 153
Anti-TPO antibody (IU/mL)	185.4 ± 215.7	< 5.0 - > 600
Anti-TG antibody (IU/mL)	232.5 ± 275.1	< 10.0 - 946
Anti-TR antibody (IU/L)	9.47 ± 33.4	< 0.3 - 25.2
TSH	3.54 ± 6.09	< 0.03 - 29.91
fT3	3.65 ± 2.03	2.09 - 5.92
fT4	1.15 ± 0.75	0.67 - 1.74

When we determined mean ± SD of each variable including variables under the lower limit and above the upper limit, we used variables of upper and lower limit. CPR: C-peptide immunoreactivity; GAD: glutamic acid decarboxylase; fT4: free thyroxine; fT3: free triiodothyronine; IA2: islet antigen 2; TG: thyroglobulin; TPO: thyroid peroxidase; TR: thyroid stimulating hormone receptor; TSH: thyroid stimulating hormone. Normal ranges of anti-GAD antibody, anti-IA2 antibody, serum CPR, urinary CPR, anti-TPO antibody, anti-TG antibody, anti-TR antibody, TSH, fT3 and fT4 are < 1.5 U/mL, < 0.4 U/mL, 0.61 - 2.09 ng/mL, 29.2 - 167.0 μg/day, < 16 IU/mL, < 28 IU/mL, < 2.0 IU/L, 0.54 - 4.26 μIU/mL, 2.39 - 4.06 pg/mL and 0.71 - 1.52 ng/dL, respectively.

hypothyroidism with high level of anti-TPO ab and anti-TG ab [8]. Therefore, we defined the absence of diffuse goiter and/or primary hypothyroidism with positive anti-TPO ab or positive anti-TG ab as immunological Hashimoto thyroiditis. We also found an insulin-dependent female patient (urinary CPR < 0.3 μg/day) with positive anti-GAD antibody [9]. She has hypothyroidism treated by levothyroxine; however, both anti-TPO ab and anti-TG ab were negative. To grasp APS3a in detail, we picked up patients with type 1 diabetes and autoimmune diabetes showing the positivity for anti-GAD ab or anti-IA2 ab or anti-TG ab or anti-TPO ab or anti-TR ab as patients with APS3a. Both anti-GAD ab and anti-IA2 ab were negative in cases 24, 25 and 26 in Table 2; however, they were insulin-dependent and showed the positivity for anti-TPO ab and anti-TG ab, and they were included in patients with APS3a.

Our previous reports [4, 7-9] and present study revealed a remarkable female predominance in APS3a, which agreed with previous reports [10, 11]. Among patients with autoimmune diabetes, SPIDDM was the most common type of diabetes, and the positive rate of anti-GAD ab was higher than that of anti-IA2 ab. Almost 80% of patients with APS3a showed the positivity for anti-GAD ab. Almost 65% patients were treated by using insulin, and approximately 23% and 8% of patients were treated by oral anti-diabetic drugs and diet/exercise, respectively. Serum and urinary CPR ranged widely from undetectable level to hyperinsulinemic level, suggesting that patients with APS3a include insulin-dependent and hyperinsulinemic patients. These may be due to the predominance of SPIDDM as phenotype of diabetes in APS3a.

Among patients with autoimmune thyroid diseases, almost 80% of patients had possible Hashimoto thyroiditis. In patients with possible Hashimoto thyroiditis, immunological Hashimoto thyroiditis was the most common phenotype. The positive rate of anti-TPO ab was higher than that of anti-TG ab. Almost 70% of patients with APS3a showed the positivity for anti-TPO ab. Overt Hashimoto thyroiditis defined by having diffuse goiter and/or primary hypothyroidism with positive anti-TPO ab or positive anti-TG ab was observed in only 15% of APS3a patients. Hashimoto thyroiditis may also progress slowly, which was supported by the predominance of SPIDDM as phenotype of diabetes in APS3a.

Almost 20% of patients had possible Grave's disease, and 83% of patients with possible Grave's disease showed overt Grave's disease. In patients with possible Grave's disease, the positive rate of anti-TR antibody was 100%.

In this study, 92.3% of APS3a patients showed the positivity for anti-GAD ab or anti-TPO ab, which suggests that the measurement of anti-GAD ab or anti-TPO ab is the useful tool to detect APS3a.

We have to mention the limitation of our study. Although APS3a is very rare, the number of subjects studied was small. To elucidate the pathogenesis of APS3a, further studies, preferably with larger numbers of subjects, will be needed. Further, we should follow up the untreated patients with positive diabetes and thyroid-associated autoantibodies.

Conclusion

We revealed clinical, endocrinological and immunological characteristics of patients with APS3a in Japan.

Author Contributions

S.M. and H.Y. designed the research. R.Y., H.K., H.H., H.A. and H.Y. collected data. S.M. and H.Y. analyzed data, and wrote the paper. All authors read and approved the final paper.

Conflict of Interests

The authors declare that they have no conflicts of interest concerning this article.

References

1. Neufeld M, Maclaren N, Blizzard R. Autoimmune polyglandular syndromes. Pediatr Ann. 1980;9(4):154-162.
2. Anderson MS. Update in endocrine autoimmunity. J Clin Endocrinol Metab. 2008;93(10):3663-3670.

3. Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocr Rev. 2002;23(3):327-364.
4. Hamasaki H, Yanai H, Hiraishi C, Moriyama S. A significant discrepancy between endocrinological and clinical phenotype and immunological phenotype in autoimmune polyglandular syndrome type 3. J Med Cases. 2012;3(1):1-3.
5. Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. N Engl J Med. 2004;350(20):2068-2079.
6. Gray RS, Herd R, Clarke BF. The clinical features of diabetes with coexisting autoimmune thyroid disease. Diabetologia. 1981;20(6):602-606.
7. Yanai H, Okamoto S, Kunimatsu J. Autoimmune polyglandular syndrome type 3 complicated by mineralocorticoid-responsive hyponatremia of the elderly. World J Diabetes. 2010;1(4):135-136.
8. Moriyama S, Yanai H. The addition of metformin and glucagon-like peptide-1 receptor agonist or dipeptidyl-peptidase-4 inhibitor to insulin for latent autoimmune diabetes in adults. Int J Diabetes Dev Ctries 2014; 34(1):56.
9. Yoshikawa R, Sako A, Kitagawa H, Hamasaki H, Okubo T, Hiraishi C, Suzuki K, Mishima S, Yanai H. The development of central pontine myelinolysis in a type 1 diabetic patient with anti-insulin antibody and similar clinical manifestations to autoimmune polyglandular syndrome. J Endocrinol Metab. 2012;2(4-5):181-186.
10. Horie I, Kawasaki E, Ando T, Kuwahara H, Abiru N, Usa T, Yamasaki H, et al. Clinical and genetic characteristics of autoimmune polyglandular syndrome type 3 variant in the Japanese population. J Clin Endocrinol Metab. 2012;97(6):E1043-1050.
11. Ben-Skowronek I, Michalczyk A, Piekarski R, Wysocka-Lukasik B, Banecka B. Type III Polyglandular Autoimmune Syndromes in children with type 1 diabetes mellitus. Ann Agric Environ Med. 2013;20(1):140-146.
12. Kasai K. [The use and problems of diagnostic guidelines for thyroid diseases]. Nihon Naika Gakkai Zasshi. 2010;99(4):692-699.
13. Fatourechi V. Subclinical hypothyroidism: an update for primary care physicians. Mayo Clin Proc. 2009;84(1):65-71.