Sequential elevation of autoantibodies to thyroglobulin and glutamic acid decarboxylase in type 1 diabetes

Eiji Kawasaki, Jun-ichi Yasui, Masako Tsurumaru, Haruko Takashima, Toshyuki Ikeoka, Fumi Mori, Satoru Akazawa, Ikuko Ueki, Masakazu Kobayashi, Hironaga Kuwahara, Norio Abiru, Hironori Yamasaki, Atsushi Kawakami

Eiji Kawasaki, Toshiyuki Ikeoka, Department of Metabolism/Diabetes and Clinical Nutrition, Nagasaki University Hospital, Nagasaki 852-8501, Japan
Jun-ichi Yasui, Haruko Takashima, Fumi Mori, Satoru Akazawa, Ikuko Ueki, Masakazu Kobayashi, Hironaga Kuwahara, Norio Abiru, Atsushi Kawakami, First Department of Internal Medicine, Nagasaki University Graduates School of Biomedical Sciences, Nagasaki 852-8501, Japan
Masako Tsurumaru, Clinical Research Center, Nagasaki University Hospital, Nagasaki 852-8501, Japan
Hironori Yamasaki, Center for Health and Community Medicine, Nagasaki University, Nagasaki 852-8521, Japan

Author contributions: Kawasaki E performed research and wrote the paper; Yasui J, Tsurumaru M, Takashima H, Ikeoka T, Mori F, Akazawa S, Ueki I, Kobayashi M, Kuwahara H, Abiru N, Yamasaki H and Kawakami A contributed to the discussion and reviewed the manuscript.

Correspondence to: Eiji Kawasaki, MD, PhD, Department of Metabolism/Diabetes and Clinical Nutrition, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. eijikawa@nagasaki-u.ac.jp

Telephone: +81-95-8197550 Fax: +81-95-8197552
Received: June 25, 2013 Revised: August 1, 2013
Accepted: August 16, 2013
Published online: October 15, 2013

Abstract

We have previously reported the high levels of glutamic acid decarboxylase 65 autoantibodies (GAD65A) in patients with type 1 diabetes and autoimmune thyroid disease. Here we describe a 32-year-old Japanese female with a thirteen-year history of type 1 diabetes whose levels of GAD65A were elevated just after the emergence of anti-thyroid autoimmunity. At 19 years of age, she developed diabetic ketoacidosis and was diagnosed with type 1 diabetes. She had GAD65A, insulinoma-associated antigen-2 autoantibodies (IA-2A), and zinc transporter-8 autoantibodies (ZnT8A), but was negative for antibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TGAb) at disease onset. ZnT8A and IA-2A turned negative 2-3 years after the onset, whereas GAD65A were persistently positive at lower level (approximately 40 U/mL). However, just after the emergence of TGAb at disease duration of 12.5 years, GAD65A were reelevated up to 5717 U/mL in the absence of ZnT8A and IA-2A. Her thyroid function was normal and TPOAb were consistently negative. She has a HLA-DRB1*03:01/*04:01-DQB1*02:01/*03:02 genotype. Persistent positivity for GAD65A might be associated with increased risk to develop anti-thyroid autoimmunity.

© 2013 Baishideng. All rights reserved.

Key words: Autoimmune thyroid disease; Case report; Glutamic acid decarboxylase autoantibodies; Type 1 diabetes

Core tip: This paper describes a case of type 1 diabetes whose levels of glutamic acid decarboxylase 65 autoantibodies (GAD65A) were reelevated just after the emergence of anti-thyroid autoimmunity at disease duration of 12.5 years without any clinical signs of thyroid dysfunction. This case report suggests that persistent positivity for GAD65A is associated with increased risk to develop anti-thyroid autoimmunity.
INTRODUCTION

Type 1 diabetes is an autoimmune disease against pancreatic islet β cells and is often complicated with other autoimmune diseases, of which autoimmune thyroid disease (AITD) is the most frequent[1]. It has been reported that the prevalence of autoantibodies to thyroid peroxidase (TPOAb) and/or thyroglobulin (TGAb) are 15%-30% in patients with type 1 diabetes at the time of diagnosis of the disease[1,8]. Furthermore, there is heterogeneity in the natural history of AITD in patients with type 1 diabetes: AITD may be diagnosed either at diabetes onset or during the follow-up, and the measurement of TPOAb and TGAb is useful to predict the development of future AITD. We and others have previously reported the association between anti-thyroid autoimmunity and anti-islet autoantibodies, especially glutamic acid decarboxylase 65 autoantibodies (GAD65A) and zinc transporter 8 autoantibodies (ZnT8A)[4,7]. The levels and the prevalence of GAD65A are higher and more persistent in type 1 diabetic patients with AITD compared to type 1 diabetes alone[6]. Here we report a 32-year-old Japanese female with a thirteen-year history of type 1 diabetes whose levels of GAD65A were reevaluated just after the emergence of anti-thyroid autoimmunity.

CASE REPORT

A 32-year-old Japanese female had developed diabetic ketoacidosis at 19 years of age and diagnosed as type 1 diabetes. She was immediately started the intensive insulin therapy and referred to our hospital for glycemic control after one month of diabetes onset. Her past medical history was unremarkable and her family history was negative for diabetes or autoimmune diseases. Her body mass index was 19.4 kg/m² and blood pressure was 108/72 mmHg. Neither exophthalmos nor diabetic retinopathy was observed. Thyroid gland was slightly enlarged. There were no abnormal findings of the heart, lungs, or abdomen. Neurological examination was also normal. As shown in Table 1, endogenous insulin secretory capacity was decreased (Urine C-peptide 5.5 μg/d) and GAD65A (4342 U/mL; normal range < 1.5 U/mL), IA-2A (index 0.769; normal range < 0.018) and ZnT8A levels were reevaluated thereafter up to 5717 U/mL in the absence of ZnT8A and IA-2A. Ultrasound examination showed a thyroid gland of homogenous parenchyma with normal size. Furthermore, no significant elevation of TPOAb was observed and her thyroid function was normal throughout the clinical course. Her hemoglobin A1c (HbA1c) levels were maintained between 6.2% and 7.5%.

During the follow-up her GAD65A, anti-thyroid antibodies and thyroid function were monitored regularly. The GAD65A level gradually decreased and reached at 40 to 50 U/mL at > 10 years after diabetes onset. Her TPO/TGAbs remained negative and thyroid function was within normal range. However, GAD65A were reevaluated to 90 U/mL thirteen years after diabetes onset. Then we measured anti-islet autoantibodies and anti-thyroid antibodies in her stored samples (Figure 1). ZnT8A and IA-2A turned negative 2-3 years after the onset, whereas GA65A had been persistently positive at lower level. However, TGAb emerged at disease duration of 12.5 years and GAD65A levels were reevaluated thereafter up to 5717 U/mL in the absence of ZnT8A and IA-2A. Ultrasound examination showed a thyroid gland of homogenous parenchyma with normal size. Furthermore, no significant elevation of TPOAb was observed and her thyroid function was normal throughout the clinical course. Her serum C-peptide level was undetectable at disease duration of 4 years and did not change after the emergence of anti-thyroid autoimmunity.

DISCUSSION

There were many reports on the association between AITD and type 1 diabetes. However, little is known on the dynamics of the humoral autoimmunity to islet autoantigens in association with anti-thyroid autoimmunity in type 1 diabetes.
type 1 diabetic patients who have no evidence of thyroid autoimmunity at disease onset. In patients with type 1 diabetes positive for glutamic acid decarboxylase autoantibodies (GADA), a higher prevalence of thyroid antibodies was reported as compared to those without GADA\cite{5,8}. Furthermore, we have previously reported that patients with type 1 diabetes and AITD (i.e., autoimmune polyendocrine syndrome type 3; APS3) show the higher levels of GAD65A compared to patients with type 1 diabetes alone in both cross-sectional and longitudinal observations\cite{9}. Because high levels of GADA are observed in insulin-deficient patients as same as that of our case, production of GADA may not be associated with the residual β cell antigens. Furthermore, it has been reported that GAD is not only expressed in β cells but also in the thyroid gland\cite{9}. Taken together it is hypothesized that the production of GADA in patients with APS3 might be attributable to a polyclonal activation of the autoimmune system in AITD and persistent positivity for GAD65A might be associated with increased risk to develop anti-thyroid autoimmunity.

It is unknown whether organ specific autoantibodies are directly involved in the pathogenesis of AITD or whether they are just secondary to tissue destruction by thyroid-infiltrating T-cells\cite{10}. In our case, TGAb turned positive 12.5 years after the onset of type 1 diabetes. It has been questioned whether TGAb provide further diagnostic information as compared to the TPOAb in the diagnosis of AITD\cite{11,12}. However, it has been reported that female gender, older (adolescence) onset, longer duration of diabetes, and positivity for GADA were risk factors for the development of thyroid disorders\cite{13,15}. In addition, it is generally accepted that a certain type of HLA is involved in the development of type 1 diabetes and AITD\cite{15,14}. An association between AITD and HLA-DR3\cite{15} and DRB1*04-DQB1*03:01\cite{16} has been reported in Caucasian population. In addition, HLA-DRB1*03:01-DQB1*02:01 and DR4-DQB1*03:02 has also been reported to contribute to both type 1 diabetes and AITD in a study of families with both diseases\cite{17,18}. Therefore, our patient, who has HLA-DRB1*03:01-DQB1*02:01 and DRB1*04:01-DQB1*03:02 haplotypes, might be at high risk for the later development of AITD. Therefore, thyroid function test should be performed regularly in this patient for possible early diagnosis of thyroid disorders, although thyroid function is still normal.

REFERENCES

1. De Block CE, De Leeuw IH, Vertommen JJ, Rooman RP, Du Caju MV, Van Campenhout CM, Weyler JJ, Winnock F, Van Aureve J, Gorsus FK. Beta-cell, thyroid, gastric, adrenal and coeliac autoimmunity and HLA-DQ types in type 1 diabetes. *Clin Exp Immunol* 2001; 126: 236-241 [PMID: 11703366 DOI: 10.1046/j.1365-2249.2001.01668.x]

2. Burbeilo PD, Lebovitz EE, Boren KE, Bayat A, Paviol S, Wenzlau JM, Barriga KJ, Rovers M, Harlan DM, Iadarola MJ. Extrapancreatic autoantibody profiles in type 1 diabetes. *PLoS One* 2012; 7: e45216 [PMID: 23028856 DOI: 10.1371/journal.pone.0045216]

3. Barker JM, Yu J, Yu L, Wang J, Miao D, Bao F, Hoffenberg E, Nelson JC, Gottlieb PA, Rovers M, Eisenbarth GS. Autoantibody "subspecificity" in type 1 diabetes: risk for organ-specific autoimmunity clusters in distinct groups. *Diabetes Care* 2005; 28: 850-855 [PMID: 15793184 DOI: 10.2337/diabetes.28.4.850]

4. Kawasaki E, Takino H, Yano M, Uotani S, Matsumoto K, Takao Y, Yamaguchi Y, Akazawa S, Nagataki S. Autoantibodies to glutamic acid decarboxylase in patients with IDDM and autoimmune thyroid disease. *Diabetes* 1994; 43: 80-86 [PMID: 8262321 DOI: 10.2337/diabetes.43.1.80]

5. Kordonouri O, Charpentier N, Hartmann R. GADA positiv-
Kawasaki E et al. GADA and anti-thyroid autoimmunity in T1D

ity at onset of type 1 diabetes is a risk factor for the development of autoimmune thyroiditis. *Pediatr Diabetes* 2011; 12: 31-33 [PMID: 20729098 DOI: 10.1111/j.1399-5448.2010.00666.x]

6 Horie I, Kawasaki E, Ando T, Kuwahara H, Abiru N, Usa T, Yamazaki H, Ejima E, Wakazaki A. Clinical and genetic characteristics of autoimmune polyglandular syndrome type 3 variant in the Japanese population. *J Clin Endocrinol Metab* 2012; 97: E1043-E1050 [PMID: 22466347 DOI: 10.1210/jc.2011-3109]

7 Jonsdottir B, Andersson C, Carlsson A, Delli A, Forsander G, Ludvigsson J, Marcus C, Samuelsson U, Ortvist E, Lernmark A, Ivarsson SA, Larsson HE. Thyroid autoimmunity in relation to islet autoantibodies and HLA-DQ genotype in newly diagnosed type 1 diabetes in children and adolescents. *Diabetologia* 2013; 56: 1735-1742 [PMID: 23666211 DOI: 10.1007/s00125-012-2535-9]

8 Bárová H, Perusincová J, Hill M, Sterzl I, Vondra K, Masek Z. Anti-GAD-positive patients with type 1 diabetes mellitus have higher prevalence of autoimmune thyroiditis than anti-GAD-negative patients with type 1 and type 2 diabetes mellitus. *Physiol Res* 2004; 53: 279-286 [PMID: 15209535]

9 Christie MR, Brown TJ, Cassidy D. Binding of antibodies in sera from Type 1 (insulin-dependent) diabetic patients to glutamate decarboxylase from rat tissues. Evidence for antigenic and non-antigenic forms of the enzyme. *Diabetologia* 1992; 35: 380-384 [PMID: 1516767 DOI: 10.1007/BF00401206]

10 McIntosh RS, Asghar MS, Weetman AP. The antibody response in human autoimmune thyroid disease. *Clin Sci (Lond)* 1997; 92: 529-541 [PMID: 9205412]

11 Padberg S, Heller K, Usadel KH, Schumm-Draeger PM. One-year prophylactic treatment of euthyroid Hashimoto’s thyroiditis patients with levothyroxine: is there a benefit? *Thyroid* 2001; 11: 249-255 [PMID: 11327616 DOI: 10.1089/107501750159651]

12 Kordonouri O, Klinghammer A, Lang EB, Grütters-Kieslich A, Grabert M, Hoff RW. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. *Diabetes Care* 2002; 25: 1346-1350 [PMID: 12145233 DOI: 10.2337/diacare.25.8.1346]

13 Kawasaki E, Gill RG, Eisenbarth GS. Type 1 diabetes mellitus. In: Eisenbarth GS Molecular mechanisms of endocrine and organ specific autoimmunity. Austin, TX: R.G. Landes Company, 1999: 149-182

14 Brand OJ, Gough SC. Immunogenetic mechanisms leading to thyroid autoimmunity: recent advances in identifying susceptibility genes and regions. *Curr Genomics* 2011; 12: 526-541 [PMID: 22654554 DOI: 10.2174/138920211798120790]

15 Tandon N, Zhang L, Weetman AP. HLA associations with Hashimoto’s thyroiditis. *Clin Endocrinol (Oxf)* 1991; 34: 383-386 [PMID: 1676351]

16 Petrone A, Giorgi G, Mesturino CA, Capizzi M, Cascino I, Nisticò L, Osborn J, Di Mario U, Buzzetti R. Association of DRB1*04-DQB1*0301 haplotype and lack of association of two polymorphic sites at CTLA-4 gene with Hashimoto’s thyroiditis in an Italian population. *Thyroid* 2001; 11: 171-175 [PMID: 11288988 DOI: 10.1089/107501750159651]

17 Levin L, Ban Y, Concepcion E, Davies TF, Greenberg DA, Tomer Y. Analysis of HLA genes in families with autoimmune diabetes and thyroiditis. *Hum Immunol* 2004; 65: 640-647 [PMID: 15219384 DOI: 10.1016/j.humimm.2004.02.026]

18 Golden B, Levin L, Ban Y, Concepcion E, Greenberg DA, Tomer Y. Genetic analysis of families with autoimmune diabetes and thyroiditis: evidence for common and unique genes. *J Clin Endocrinol Metab* 2005; 90: 4904-4911 [PMID: 15928253]

P- Reviewers Markopoulos AK, Sanlioglu AD
S- Editor Song XX L- Editor A E- Editor Liu XM
