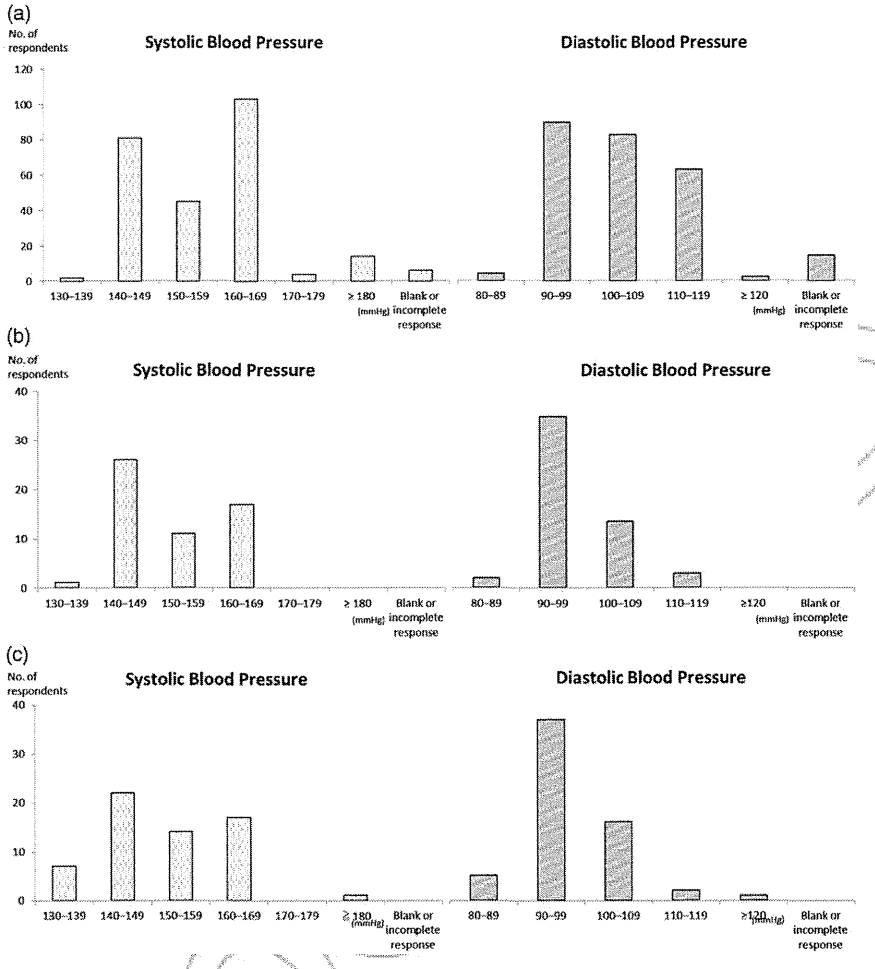

Figure 3. Distribution of threshold blood pressure levels to initiate antihypertensive therapy. (a) Chief obstetricians For systolic blood pressure, 40.2% (103/256), 31.6% (81/256) and 17.6% (45/256) of chief obstetricians indicated 160–169, 140–149 and 150–159 mmHg, respectively. For diastolic blood pressure, 35.2% (90/256), 32.4% (83/256) and 24.6% (63/256) indicated 90–99, 100–109 and 110–119 mmHg, respectively. (b) Chief internists For systolic blood pressure, 47.3% (26/55), 30.9% (17/55) and 20.0% (11/55) of chief internists indicated 140–149, 160–169 and 150–159 mmHg, respectively. For diastolic blood pressure, 65.4% (36/55) and 25.5% (14/55) responded with 90–99 and 100–109 mmHg, respectively. (c) Hypertension specialists For systolic blood pressure, 36.1% (22/61), 27.9% (17/61) and 23.0% (14/61) of hypertension specialists indicated 140–149, 160–169 and 150–159 mmHg, respectively. For diastolic blood pressure, 60.7% (37/61) and 26.2% (16/61) responded with 90–99 and 100–109 mmHg, respectively. Physicians who routinely prescribed antihypertensives to patients with postpartum hypertension responded to this question. *For an explanation of chief obstetricians (a), chief internists (b) and hypertension specialists (c), see the footnotes to Figure 1.

Table 3. Drug therapy for postpartum hypertension.

	Chief obstetricians[b]		Chief internists[b]		Hypertension specialists[b]	
	No.	Proportion (%)	No.	Proportion (%)	No.	Proportion (%)
Panel a: Class of drugs prescribed to treat postpartum hypertension[a]						
Calcium channel blocker	265	61.6	60	54.1	76	49.0
Methyldopa	90	20.9	22	19.8	34	21.9
Hydralazine	40	9.3	10	9.0	13	8.4
αβblocker	15	3.5	6	5.4	10	6.5
βblocker	3	0.7	3	2.7	5	3.2
αblocker	1	0.2	1	0.9	2	1.3
Diuretics	1	0.2	2	1.8	3	1.9
Angiotensin-converting enzyme inhibitor	5	1.2	2	1.8	4	2.6
Angiotensin receptor blocker	9	2.1	5	4.5	8	5.2
Combination drug	1	0.2	0	0	0	0
Total	430	100	111	100	155	100
Panel b: Calcium channel blockers indicated in the questionnaire response Nifedipine and amlodipine accounted for the majority of calcium channel blockers.						
Agent						
Nifedipine	210	88.2	28	58.3	31	63.3
Amlodipine	16	6.7	18	37.5	16	32.7
Nicardipine	10	4.2	0	0	1	2.0
Cilnidipine	2	0.8	2	4.2	1	2.0
Total	238	100	48	100	49	100

[a]Calcium channel blockers were the most widely prescribed in departments of internal medicine and obstetrics, followed by central nervous system depressants and vasodilators.
This question was applicable only to the physicians who routinely prescribed antihypertensives to treat postpartum hypertension. Multiple choices were allowed.
[b]For an explanation of chief obstetricians, chief internists and hypertension specialists, see footnotes to Figure 1.

(6) Please choose the types of antihypertensives that you regularly prescribe (multiple responses allowed). (This question was applicable only to the physicians who responded positively to Question No. 4.)

Calcium channel blockers were most widely prescribed in departments of internal medicine and obstetrics, followed by central nervous system depressants and vasodilators (Table 3, panel a). Calcium channel blockers were used by 61.6% (265/430) of chief obstetricians, 54.1% (60/111) of chief internists and 49.0% (76/155) of hypertension specialists. Central nervous system depressants were prescribed by 20.9% (90/430) of chief obstetricians, 19.8% (22/111) of chief internists and 21.9% (34/155) of hypertension specialists. Vasodilators were administered by 9.3% (40/430) of chief obstetricians, 9.0% (10/111) of chief internists and 8.4% (13/155) of hypertension specialists. Alpha-beta-blockers were reported by 3.5% (15/430) of chief obstetricians, 5.4% (6/111) of chief internists and 6.5% (10/155) of hypertension specialists.

Table 4. Use of antihypertensive agents in breastfeeding patients.

	Allow	Not Allow	Other	Total
Chief obstetricians[a]	224 (87.5%)	12 (4.7%)	20 (7.8%)	256 (100%)
Chief internists[a]	38 (69.1%)	14 (25.5%)	3 (5.5%)	55 (100%)
Hypertension specialists[a]	28 (45.9%)	20 (32.8%)	13 (21.3%)	61 (100%)

A total of 85.5% (224/256) of chief obstetricians, 69.1% (38/55) of chief internists and 45.9% (28/61) of hypertension specialists allowed breastfeeding in patients receiving antihypertensive medications, while 4.7% (12/256), 25.5% (14/55) and 32.8% (20/61), respectively, recommended discontinuation of lactation for patients who were on antihypertensive treatment.

This question was applicable only to the physicians who routinely prescribed antihypertensives to treat postpartum hypertension. Figures not enclosed in parentheses represent the numbers of respondents, and the percentages in parentheses their proportions.

[a]For an explanation of chief obstetricians, chief internists and hypertension specialists, see footnotes to Figure 1.

Angiotensin-converting enzyme inhibitors were prescribed by 1.2% (5/430) of chief obstetricians, 1.8% (2/111) of chief internists and 2.6% (4/155) of hypertension specialists, while angiotensin receptor blockers were used by 2.1% (9/430), 4.5% (5/111) and 5.2% (8/155), respectively (Table 3, panel a).

Nifedipine and amlodipine accounted for the majority of calcium channel blockers. Nifedipine was prescribed by 88.2% (210/238) of chief obstetricians, 58.3% (28/48) of chief internists and 63.3% (31/49) of hypertension specialists, while amlodipine was administered by 6.7% (16/238), 37.5% (18/48) and 32.7% (16/49), respectively (Table 3, panel b).

(7) Question: What guidance do you give concerning breastfeeding when you prescribe antihypertensive agents to patients with postpartum hypertension?

A total of 85.5% (224/256) of chief obstetricians, 69.1% (38/55) of chief internists and 45.9% (28/61) of hypertension specialists allowed breastfeeding in patients receiving antihypertensive medications, while 4.7% (12/256), 25.5% (14/55) and 32.8% (20/61), respectively, recommended discontinuation of lactation for patients who were on antihypertensive treatment (Table 4).

DISCUSSION

Awareness of Long-term Risks and Clinical Care for Women with HDP

In the Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women-2011 Update (21) published by the American Heart Association, a history of abnormal pregnancy was identified as a risk factor for cardiovascular disease. The guidelines underline the importance of appropriate postpartum referral by the obstetrician to a primary care physician or hypertension specialist to ensure that risk factors can be carefully monitored and controlled after pregnancy. The current study showed that

among the leading practicing obstetricians and internists in Japan, HDP are recognized as a risk factor for chronic hypertension and cardiovascular disease. At the same time, this study showed that over a third of chief obstetricians terminated their postpartum follow-up of HDP patients without referring them to primary care physicians or hypertension specialists. The finding that only 41% of chief internists and 36% of hypertension specialists were routinely seeing patients with postpartum hypertension suggested that such patients were not fully aware of the implications of HDP, and that there is a lack of appropriate referral by the obstetricians. This could be partly attributable to the fact that postpartum hypertension often resolves shortly after delivery. Pregnancy represents a metabolic "stress test" to predict cardiovascular events in women (22). In order to prevent future development of disease, it is important to keep track of women whose high cardiovascular risk has been unmasked by pregnancy-related events. For this purpose, coordination between the departments of obstetrics and internal medicine, such as a referral system that will enable smooth transition of high-risk patients from the obstetrician to the primary care physician or to the specialist, is necessary. At the same time, our results suggested the need to create effective education and long-term monitoring programs for women at high cardiovascular risk.

Drug Therapy for Postpartum Hypertension

Compared to internists, obstetricians applied higher blood pressure thresholds for prescribing drug therapy. This reflected the likelihood of obstetricians preferring to avoid medication during breastfeeding and that they hold the view that blood pressure can change significantly in the early postpartum period. The literature reports a variety of criteria for starting drug therapy in patients with postpartum hypertension. A systematic review found that antihypertensive therapy should be advised for severe hypertension (systolic blood pressure $\geq$ 170 mmHg or diastolic blood pressure $\geq$110 mmHg) to prevent maternal cerebral hemorrhage and other acute vascular injuries (6). However, there was no consensus regarding antihypertensive interventions for treating mild-to-moderate hypertension (systolic blood pressure 140 to 169 mmHg, or diastolic blood pressure 90 to 109 mmHg) (6). In the 1997 Canadian Hypertension Society Consensus report (23), initiation of antihypertensive drug treatment was recommended for severe hypertension and mild-to-moderate hypertension with a variety of comorbid conditions. The guidelines reported no particular criteria for the threshold to initiate therapy or treatment goal based on the study of Japan Society for the Hypertension in Pregnancy, the national high blood pressure education program work group set up by NIH (24) and the consensus statement by the ASSHP (25). This might possibly reflect the general idea that postpartum hypertension is only temporary, and that blood pressure will decrease within a certain time. However, studies revealed that approximately one-fifth of women with preeclampsia later developed chronic hypertension (11,26). In addition, a systematic literature review found that preeclampsia increased the risk of vascular disease and chronic hypertension (17). These findings emphasize the need to extend short-term postpartum care into a long-term follow-up and management program.

Our survey showed that patients with postpartum hypertension were mostly frequently treated with calcium channel blockers by obstetricians and internists, followed by centrally acting sympatholytic drug methyldopa and vasodilator hydralazine. The profile of postpartum antihypertensive use was similar to that of the antepartum period. The wide acceptance of calcium channel blockers in pregnancy was probably attributable to their excellent blood pressure-lowering effect and that nifedipine have not been contra-indicated in women after 20 weeks of gestation in Japan. Our data suggested that obstetricians preferred nifedipine to amlodipine, whereas internists favored amlodipine more than obstetricians. Appropriate antihypertensives should be chosen for the breastfeeding mother, taking into consideration the effects on maternal blood pressure levels, exposure of the lactating child to the drug, and the mother's daily life patterns. These factors suggested that calcium channel blockers were drugs of choice for breastfeeding mothers. Use of the centrally acting sympatholytic drug methyldopa in postpartum patients should be accompanied by careful consideration. The NICE advised that methyldopa should be replaced with an alternative drug for the management of postpartum hypertension because of associated postpartum depression (27).

Our data revealed a discrepancy of opinion between obstetricians and internists regarding the use of antihypertensives during breastfeeding. Obstetricians generally supported it, whereas internists were more cautious. Breastfeeding has benefits for infants with respect to nutrition, gastrointestinal function and host defense (28). Recent research showed that breast milk was superior to infant artificial formula in terms of reduction in systolic blood pressure (29,30), risk of type 2 diabetes mellitus (31) and obesity (32) of infants in later life. A generational study showed that children born to mothers with HDP had higher systolic and diastolic blood pressures at the age of nine years (33). These findings highlight the benefits of breast-fed children. Also, breastfeeding provides metabolic advantages to the mother. Recent studies of the relationship between breastfeeding and cardiovascular risk factors reported a lower prevalence of lipid metabolism abnormalities (34) and lower blood levels of glucose and insulin (35) in mothers with a history of breastfeeding than those without. In addition, lower incidences of metabolic syndrome were observed in mothers with longer lactation periods (36).

Breastfeeding offers a significant advantage in reducing cardiovascular risks in both mothers and children; it should therefore be recommended, in particular, for patients with HDP. If the mother requires antihypertensive therapy, appropriate drugs that enable breastfeeding, while achieving effective blood pressure control should be selected. The use of such medications will contribute to reducing future risks to the mother and her children.

CONCLUSION

Pregnancy and childbirth represent an excellent occasion to identify women who are at high risk of cardiovascular disease. An adequate referral system that enables smooth transfer to a local primary care physician or hypertension specialist will help reduce the likelihood of future cardiovascular disease.

ACKNOWLEDGEMENTS

The authors would like to thank obstetricians and internists who responded to many questionnaire of this study. They would also like to thank Dr Julian Tang from the Department of Education for Clinical Research, NCCHD, for reviewing this manuscript.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

This study was conducted as part of the project titled "Prevention of Diabetes Mellitus and Metabolic Syndrome in Women and offspring in the view of pregnancy-associated events" funded under the FY2012 Health and Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare of Japan.

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Clinical Immunology (2015) 156, 36–42

available at www.sciencedirect.com

Clinical Immunology

www.elsevier.com/locate/yclim

Disease specificity of anti-tryptophan hydroxylase-1 and anti-AIE-75 autoantibodies in APECED and IPEX syndrome

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Received 8 September 2014; accepted with revision 30 October 2014
Available online 8 November 2014

KEYWORDS
Tryptophan hydroxylase;
AIE-75;
Villin;
APECED;
IPEX syndrome

Abstract Autoantibodies to autoimmune enteropathy-related 75 kDa antigen (AIE-75) and villin are disease markers of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome which is characterized by a peripheral tolerance defect. On the other hand, anti-tryptophan hydroxylase-1 (TPH-1) antibodies are detected in autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED), a central tolerance defect, especially when complicated with gastrointestinal dysfunction. However, to date, anti-AIE-75 and anti-villin antibodies or anti-TPH-1 antibodies have not been tested in APECED or IPEX syndrome, respectively. In the present study, we confirmed the disease specificity of both anti-AIE-75 and anti-TPH-1, although anti-villin antibodies were detected in some patients with APECED. Our observation suggests that immunotolerance to AIE-75 depends on the peripheral mechanism, whereas the tolerance to TPH-1 depends on the central mechanisms.

Abbreviations: AIE-75, autoimmune enteropathy-related 75 kDa antigen; AIRE, autoimmune regulator; APECED, autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy; CMC, chronic mucocutaneous candidiasis; FOXP3, forkhead box transcription factor 3; GST, glutathione-S-transferase; IPEX syndrome, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; mTEC, medullary thymic epithelial cells; TPH-1, tryptophan hydroxylase-1; Treg, regulatory T; TSA, tissue-specific antigen

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http://dx.doi.org/10.1016/j.clim.2014.10.010
1521-6616/

1. Introduction

Both T cells and B cells acquire their diversification by random recombination of T cell receptor (TCR) and B cell receptor (BCR) genes, respectively. This results in generation of a significant number of self-reactive T and B lymphocytes, but the majority of them are eliminated or suppressed by several mechanisms that contribute to immunological tolerance [1,2]. Autoimmune regulator, *AIRE*, is involved in the intrathymic expression of tissue-specific antigens (TSAs) and plays a critical role in the negative selection of self-reactive T cells, also known as central immunotolerance [1]. Although some self-reactive T cells escape negative selection and efflux to periphery, they are in anergic state or inactivated by regulatory T (Treg) cells [2,3]. Forkhead box transcription factor 3, *FOXP3*, is a master gene in the development of Treg cells and contributes to peripheral dominant immunotolerance [2,3]. Failure of the immunotolerance mechanisms causes multiple organ-specific autoimmune disorders. Mutations of *AIRE* gene result in autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED) which is characterized by autoimmunity to endocrine tissues such as parathyroid gland and adrenal gland, and to cytokines critical for antifungal immunity, interleukin-17 [1]. Mutations of *FOXP3* genes cause immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, which is characterized by autoimmune enteropathy and endocrinopathies such as type-1 diabetes mellitus and thyroiditis [4,5].

We have identified autoimmune enteropathy-related 75 kDa antigen (AIE-75) and an actin binding protein, villin, as target autoantigens of enteropathy in IPEX syndrome [6–8]. Recent studies have confirmed the high specificity and sensitivity of these two antibodies regardless of ethnicity [9,10]. On the other hand, gastrointestinal dysfunction is observed in about 10% of APECED patients. Autoantibodies against tryptophan hydroxylase (TPH)-1 are detected in 89% of the patients with APECED complicated by gastrointestinal dysfunction and 34% of the patients without gastrointestinal complications [11–14]. Recently, Sayar et al. have suggested that some cases of APECED with gastrointestinal dysfunction could mimic IPEX syndrome [15]. Nevertheless there have been no studies that tested anti-AIE-75 or anti-villin antibodies in APECED and anti-TPH-1 antibodies in IPEX syndrome. In the present study, we examined autoantibodies to TPH-1, AIE-75 and villin in APECED and IPEX syndrome.

2. Materials and methods

2.1. Patients and sera

We investigated 7 patients with IPEX syndrome (6 Japanese and 1 American) and 23 patients with APECED (20 Italian, 2 Japanese and 1 American) (Tables 1 and 2). This work was approved by the Institutional Review Board of Hokkaido University Hospital with written informed consent from the patients or guardians. Clinical and laboratory features and genetic mutations of some patients have previously been reported [8,14,16,17]. Among the twenty Italian patients with APECED, 10 were positive for anti-TPH-1 antibodies as judged from immunoprecipitation (IP-positive), whereas the other 10 were negative for the antibodies (IP-negative) [13,14]. Sera from 2 Japanese and 1 American (Irish/Spanish) patients have not been tested for the antibodies by IP (IP-NT). Sera were obtained from the patients and stored at −20 °C until use.

2.2. Production of recombinant fusion proteins

Recombinant human TPH-1 was expressed as a fusion protein with glutathione-S-transferase (GST). Briefly, the primer pair was designed to amplify whole coding region with *BamHI* restriction site at the 5′ end and *XhoI* site at the 3′ end as the following; 5′-GGATCCATGATTGAAGACAATAAGGAG-3′, and 5′-CTCGAGTTAGATACTCGGCTTCCTGCT-3′. Complimentary DNA encoding TPH-1 (NM_004179) was amplified by polymerase chain reaction (PCR) using λgt11 human duodenal cDNA library (BD Biosciences Clontech, Palo Alto, CA) as a template. The PCR product was inserted into pCR2.1-TOPO TA cloning vector (Invitrogen, Carlsbad, CA), digested with both *BamHI* and *XhoI* and then subcloned into a GST fusion protein expression vector, pGEX4T-2. *Escherichia coli, BL-21*, was transformed with the plasmid containing correct nucleotide sequence of TPH-1. Fusion protein, GST-TPH-1, was expressed in the presence of 0.5 mM isopropylthiogalactoside (IPTG) and purified with glutathione-sepharose beads (Amersham Biosciences, Piscataway, NJ). Recombinant AIE-75 and GST-villin were expressed and used for immunoblotting as previously reported [7,8].

2.3. Immunoblotting

A 60 ng of the recombinant antigens was subjected to electrophoresis on sodium dodecyl sulfate-polyacrylamide gel, and electrically transferred to polyvinylidene difluoride membrane (Millipore, Bedford, MA). After blocking with 5% skim milk, the membranes were incubated with 1:200 diluted rabbit polyclonal anti-TPH-1 antibody (Sigma Aldrich), 1:1000 diluted goat anti-GST antibody (Amersham Biosciences), or 1:80–1:5120 diluted human sera. Human sera were diluted with Tris-buffered saline containing 0.1% Tween-20 (TBST) and crude lysate prepared from *E. coli* expressing GST to block potential cross-reactivity with GST or components of *E. coli* except for some experiments. After incubation with primary antibodies, membranes were washed with TBST three times and incubated with diluted horseradish peroxidase (HRP)-conjugated goat anti-human IgG at 1:5000 (Biosource, Camarillo, CA), HRP-conjugated goat anti-rabbit IgG at 1:2000 (Biosource) or HRP-conjugated rabbit anti-goat IgG (Biosource) at 1:2000 for 1 h at room temperature. All the secondary antibodies were diluted with TBST. After washing with 50 mM Tris–HCl pH 7.6, immunoreactive bands were detected by 3,3′-diaminobenzidine (Sigma, St. Louis, MO) and nickel ion (0.03% $NiCl_2$).

3. Results

3.1. Production of recombinant fusion protein

The fusion protein was immunoreactive on blots with either anti-GST or anti-TPH-1 antibody (Fig. 1). The apparent

Table 1 Clinical and laboratory features of patients with APECED.

Case no.	Clinical manifestation	Intestinal dysfunction	Autoantibodies	Anti-TPH-1 Abs by IP [binding index]	Ethnicity
1	AD, HP, CMC, M	Yes	Not tested	Not tested	Japanese
2	HP, CMC, AIH	No	Not tested	Not tested	Japanese
3	AD, HP, CMC, POF, K	Yes	IFNωAbs	84.13	Italian
4	AD, HP, CMC, EH, demyelinating polyneuropathy	No	IFNωAbs, AADC	167.6	Italian
5	AD, HP, AIT, POF, Ch, CTD, AG, PA, AIH, M, K, ND, A	Yes	IFNωAbs, AADC	90.1	Italian
6	AD, HP, CMC, AIT, POF, AG, PA, Co	No	IFNωAbs, AADC	200	Italian
7	AD, HP, CMC, POF, CTD, AG, PA, K, Va	No	IFNωAbs, AADC	56.7	Italian
8	AD, HP, CMC, AG, M, K, V, A	Yes	IFNωAbs, AADC	137	Italian
9	AD, HP, CMC, AIT, GHD, AG, M, Co, V	Yes	IFNωAbs, AADC	114.9	Italian
10	AD, HP, CMC, POF, AG, AIH, A	No	IFNωAbs, AADC	74.4	Italian
11	AD, HP, CMC, ND	No	IFNωAbs	7.7	Italian
12	AD, HP, CMC, ND, A	No	IFNωAbs, AADC	201.22	Italian
13	AD, HP, CMC, POF, Co, CTD, AG	No	AADC	Negative	Italian
14	HP, POF	No	IFNωAbs	Negative	Italian
15	AD, CMC, POF, ND, A, EH	No	IFNωAbs	Negative	Italian
16	AD, HP, CMC, POF	No	IFNωAbs, AADC	Negative	Romanian
17	AD, HP, CMC, POF, GHD, ND, EH	Yes	IFNωAbs	Negative	Italian
18	AD, HP, CMC,	No	IFNωAbs	Negative	Italian
19	AD, HP, AG	No	IFNωAbs	Negative	Italian
20	AD, HP, CMC, Ch, CTD, AG, A, TMC	No	IFNωAbs, AADC	Negative	Italian
21	AD, HP	No	IFNωAbs	Negative	Italian
22	AD, HP, CMC, AIH	No	IFNωAbs, AADC	Negative	Italian
23	AIH, AIT, GN, IDDM	Yes	Not tested	Not tested	Irish/ Spanish

Abbreviations; AADC, antibodies to aromatic L-amino acid decarboxylase; IFNωAbs, antibodies to interferon-ω; Abs, antibodies; A, alopecia; AD, Addison's disease; AG, atrophic gastritis; AIH, autoimmune hepatitis; AHA, autoimmune hemolytic anemia; AIT, autoimmune thyroiditis; As, asplenia; CD, Celiac Disease; Ch, cholelithiasis; CMC, chronic mucocutaneous candidiasis; Co, constipation; CTD, connective tissue disease; EH, enamel hypoplasia; GHD, growth hormone deficiency; GN: glomerulonephritis; HP, hypoparathyroidism; IDDM: insulin-dependent diabetes mellitus; IP, immunoprecipitation; K, keratoconjunctivitis; M, malabsorption; ND, nail dystrophy; PA, pernicious anemia; POF, premature ovarian failure; Ps, psoriasis; TMC, tympanic membrane calcification; TIN, tubulointerstitial nephritis; V, vitiligo; Va, vasculitis.

molecular size of the fusion protein was approximately 75 kDa, consistent with the sum of GST (26 kDa) and TPH-1 (51 kDa).

3.2. Autoantibodies to TPH-1

As shown in Fig. 2A, an IP-NT serum (APECED-2) reacted with GST-TPH-1 but not with GST alone. GST-TPH-1 reacted with 8 of 10 IP-positive APECED patients, but none of the sera from 10 IP-negative or 2 IP-NT patients (Fig. 2B and data not shown). However, there was no correlation between the titers of antibodies measured by IP and immunoblot (Fig. 3). On the other hand, none of the sera from 7 patients with IPEX reacted with GST-TPH-1 (Fig. 4).

3.3. Reactivity of the sera to AIE-75 and villin

Anti-AIE-75 antibodies were detected in 5 of 7 patients with IPEX syndrome but not in any patients with APECED (Fig. 5 and Table 2). Anti-villin antibodies were detected in 4 of 7 patients with IPEX syndrome and 3 of 23 patients with APECED (Fig. 6 and Table 2).

4. Discussion

In the present study, we demonstrate that anti-AIE-75 antibodies and anti-TPH-1 antibodies are specific to IPEX syndrome and APECED, respectively. These confirm the specificity and diagnostic value of anti-TPH-1 and anti-AIE-75 autoantibodies in APECED and IPEX, respectively [6–14]. On the other hand, anti-villin antibodies were detected in sera from 3 of 23 patients with APECED (1 with and 2 without GI dysfunction). Low levels (1:160 or lower) of anti-villin antibodies are also detected in some patients with other collagen vascular diseases such as SLE and mixed connective tissue disease [8]. Thus, villin could be highly immunogenic, and anti-villin autoantibodies are produced in several autoimmune diseases. Anti-TPH-1 antibodies were detected in 8 of 10 IP-positive patients with APECED. Interestingly, there were no correlations between the titers determined by immunoblotting and the binding index by the IP assay. IP assays using deletion mutants of TPH-1 have revealed three major epitopes of the antigen [13]. Although the conformation of antigens is preserved in IP, immunoblot detects antibodies against linear peptide sequences of denatured antigens. Our result suggests that

Table 2 Clinical and laboratory features of IPEX patients.

Case no.	Clinical manifestation	Anti-AIE-75 Abs (IB)	Anti-villin Abs (IB)	Ethnicity	Outcome
1	Diarrhea	1:80	1:2560	Japanese	Alive
2	Diarrhea, NS, T1DM	1:640	Negative	Japanese	Alive
3	AHA, Diarrhea, AIT, TIN	1:320	1:320	Japanese	Died
4	Diarrhea, AIT, TIN	1:160	1:320	Japanese	Died
5	Diarrhea	Negative	1:160	Japanese	Died
6	Alopecia, psoriasiform dermatitis, Diarrhea	Negative	Negative	Caucasian	Alive
7	Diarrhea, food allergy, eczema, NS, AIH	1:2560	Negative	Japanese	Alive

Abbreviations; AIE-75, autoimmune enteropathy-related 75 kDa antigen; Abs, antibodies; AHA, autoimmune hemolytic anemia; AIT, autoimmune thyroiditis; AIH, autoimmune hepatitis; NS, nephrotic syndrome; TIN, tubulointerstitial nephritis.

the autoantibodies to conformation of TPH-1 are dominant in some patients with APECED, whereas those to linear peptides are dominant in the others. However, our study could not clarify whether autoantibodies against the conformational or linear epitopes are associated with clinical GI tract dysfunction.

Most of APECED patients enrolled in our study were Italian, whereas most IPEX patients were Japanese. Both anti-AIE-75 and anti-villin antibodies are prevalent in patients with IPEX regardless of their ethnicities [7–10]. On the other hand, although the most frequent mutation in *AIRE* gene differs between races, genotype–phenotype correlations have not been clarified except for the association between large truncations of AIRE and candidiasis [18]. Thus, the influence of the bias in the ethnicities on our results remains unclear.

APECED and IPEX syndrome share several common features such as type-1 diabetes mellitus and thyroiditis, however, Addison's disease and hypoparathyroidism are prevalent in APECED but not in IPEX syndrome [1,3,19]. AIE-75 and villin are expressed in the duodenal epithelial cells, whereas expression of TPH-1 is limited to enterochromaffin cells in the intestine [7,8,14]. These are consistent with histopathological findings; severe inflammation is associated with villous atrophy of the duodenal tissue in IPEX syndrome, whereas only minimal inflammation and loss of enterochromaffin cells without apparent villous atrophy are observed in the intestine of anti-TPH-1 antibody-positive APECED [3,14,20]. Coincidence of the target cells and distribution of the autoantigens suggest a pathological role of antigen-specific autoimmunity in the development of enteropathy in both diseases. Because all of the three antigens are cytoplasmic proteins, circulating autoantibodies may not directly bind them. Indeed, interstitial nephritis is not necessarily observed in IPEX syndrome positive for autoantibodies to these antigens despite the expression of both AIE-75 and villin in the renal tubules [7,8]. Furthermore, anti-TPH-1 antibodies are positive in one-third of the cases of APECED without gastrointestinal dysfunction [11–14]. Given that autoreactive T cells share the same antigen-specificity with autoantibodies in autoimmune diseases [21–23], autoreactive T cells likely play a critical role in the tissue- or cell type-specific destruction in both diseases. Autoantibodies or autoreactive BCR may bind cytoplasmic antigens that had leaked from apoptotic or necrotic cells and facilitate the activation of T cells by antigen presenting cells [24]. Indeed, depletion of B cells in *Scurfy* mice, counterparts of human IPEX syndrome, reduces tissue damages [25]. Furthermore, follicular Treg cells which are derived from thymic naturally occurring Treg cells directly suppress autoreactive B cells in the peripheral lymphoid tissues [26–29]. As a result, Treg cell dysfunction allows the accumulation of autoreactive B cells in IPEX syndrome [30].

AIRE is expressed mainly in the medullary thymic epithelial cells (mTEC), acts as a transcription factor responsible for the

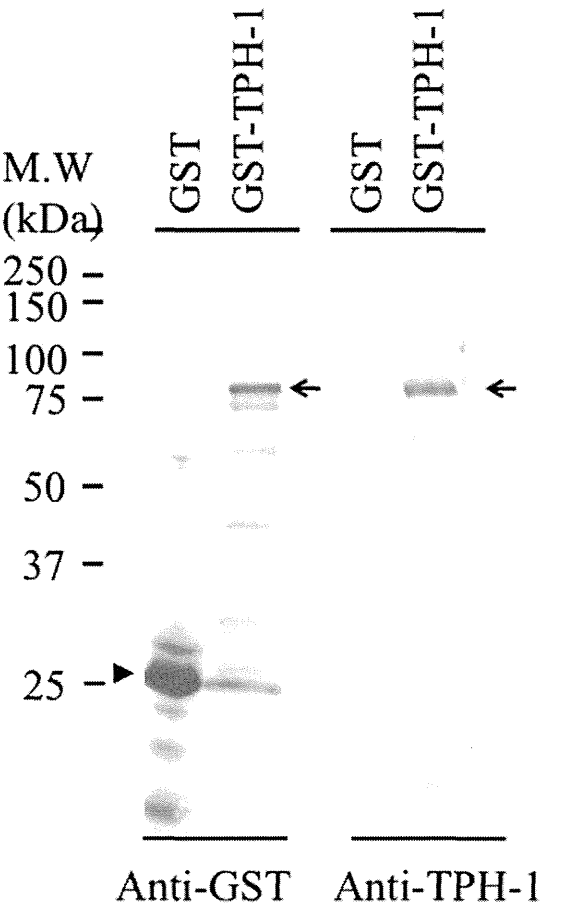

Figure 1 Expression of recombinant GST-TPH. GST or GST-TPH-1 is immunoblotted with anti-GST (A) or anti-TPH-1 (B) antibodies. In this experiment, the serum was diluted with TBST without *E. coli* extract. Both GST and GST-TPH-1 reacted with anti-GST antibodies, whereas only GST-TPH-1 reacted with anti-TPH-1 antibodies. Arrow and arrowhead indicate recombinant GST-TPH-1 and GST alone, respectively.

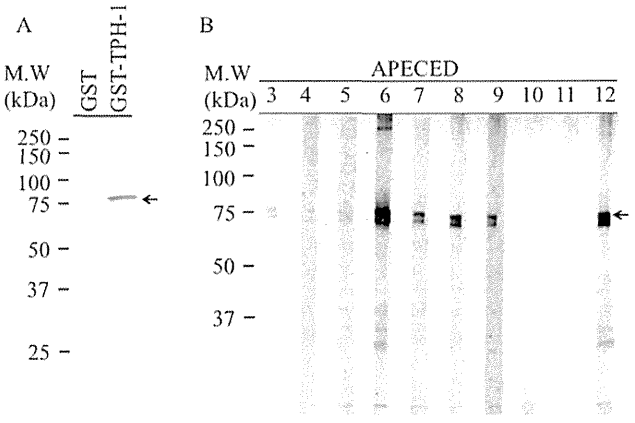

Figure 2 Anti-GST-TPH-1 antibodies in sera from APECED patients. (A) The serum of APECED-2 reacted with GST-villin but not GST alone. In this experiment, the serum was diluted by TBST without *E. coli* extract. (B) GST-TPH-1 reacted with 10 APECED sera (cases 3–12) in which the autoantibodies have been detected by immunoprecipitation. Anti-TPH-1 antibodies were not detected in cases 10 and 11 by immunoblotting. Arrows indicate GST-TPH-1.

thymic expression of TSAs, and contributes to the elimination of self-reactive T cells [1]. In addition, *AIRE* is expressed in the peripheral lymphoid tissues, and accordingly, may play a role in the peripheral tolerance. On the other hand, *FOXP3* is a master gene of Treg cells which play a central role in peripheral immunotolerance [2,3]. Thus, immunotolerance mechanisms may differ between autoantigens; tolerance to TPH-1 depends on intrathymic negative selection or AIRE-dependent peripheral tolerance, whereas tolerance to AIE-75 depends on Treg cells. Both TPH-1 and villin are expressed in mTEC of *AIRE*-deficient mice, although the expression of AIE-75 has not been studied [31]. Some target autoantigens associated with APECED are also expressed in mTEC in *AIRE*-independent manners [32–34]. Thus, AIRE must have roles in negative selection through a mechanism distinct from intrathymic transcription of TSA, e.g., antigen presentation by mTEC or interdigitating reticular cells in the peripheral lymphoid organs [35]. Otherwise, expression of TSAs in human mTEC may be different from those in mice. To date, whether AIRE contributes to the selection of Treg cells in the thymus is still controversial [34,36]. However, given the severe clinical features of IPEX syndrome compared with APECED, at least some of Treg cells may develop independent of AIRE.

5. Conclusions

Autoantibodies to AIE-75 and TPH-1 could be used for the differential diagnosis of IPEX syndrome and APECED. Coincidence of the distribution of autoantigens and target cell types

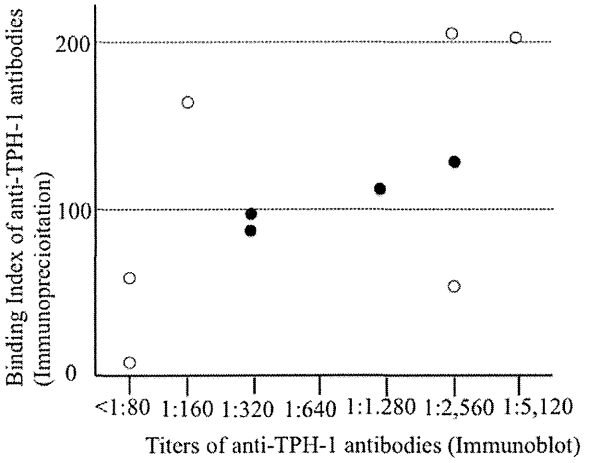

Figure 3 Anti-TPH-1 measured by immunoprecipitation and immunoblotting. The titers of anti-TPH-1 antibodies in APECED patients were compared with the binding unit of the antibodies measured by immunoprecipitation. There is no significant correlation between the binding unit by immunoprecipitation and titers by immunoblotting (Spearman's rank correlation coefficient; rs = −0.56, p = 0.088). Closed circles indicate patients with gastrointestinal manifestations.

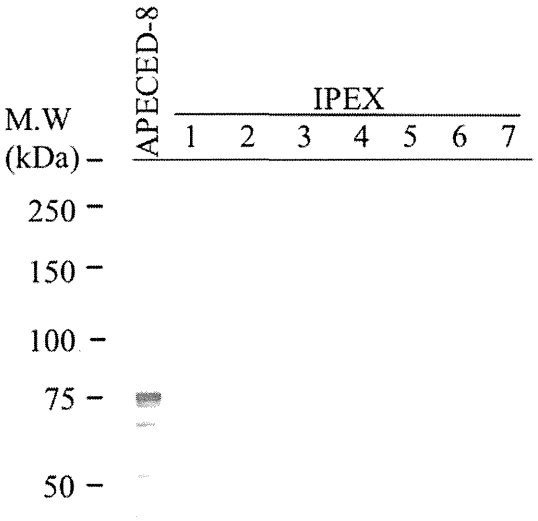

Figure 4 Autoantibodies to TPH-1 are specific to APECED. GST-TPH-1 reacted with the serum of APECED-8 but none of IPEX syndrome. All the sera were diluted with TBST containing extracts of *E. coli* expressing GST.

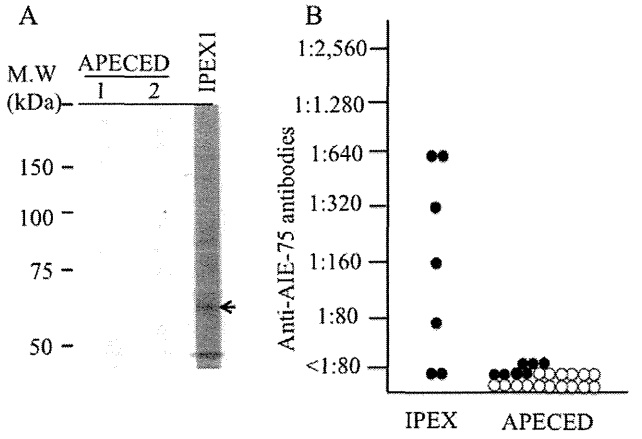

Figure 5 Autoantibodies to AIE-75 are specific to IPEX syndrome. (A) AIE-75 reacted with the serum from IPEX-1 but not with sera from APECED-1 and -2. (B) Anti-AIE-75 antibodies were detected in 5 of 7 sera from IPEX syndrome patients but none of 23 APECED sera. An arrow indicates recombinant AIE-75. Closed circles indicate patients with gastrointestinal manifestations.

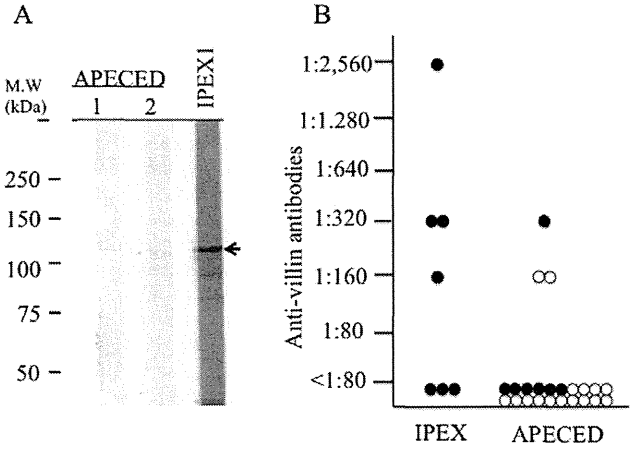

Figure 6 Autoantibodies to GST-villin. (A) GST-villin reacted with the serum from IPEX-1 but not with sera from APECED-1 and -2. The molecular weight of GST-villin is approximately 120 kDa which is consistent with that calculated from GST (26 kDa) and villin (91 kDa). (B) Anti-villin antibodies were detected in 4 of 7 sera from IPEX syndrome patients and 3 of 23 sera from APECED patients. All of the sera were diluted with TBST containing extracts of *E. coli* expressing GST. An arrow indicates GST-villin. Closed circles indicate patients with gastrointestinal manifestations.

suggests the involvement of antigen-specific mechanisms in the intestinal dysfunctions in both diseases. Immunotolerance to AIE-75 and TPH-1 may depend on the peripheral and central mechanisms, respectively.

Conflict of interest statement

The author(s) declare that there are no conflicts of interest.

Acknowledgment

The authors thank Dr. Yoichi M. Ito (Hokkaido University) for his advice on statistical analyses, and Drs. D. Nieves (Rochester University), S. Itoh (National Center for Child Health and Development), H. Tanaka (Hirosaki University), L. Whitesell (Whitehead Institute for Biomedical Research), Y. Shikama (Kanagawa Children's Medical Center) and A. Yara (Naha Municipal Hospital) for providing the sera.

This work was supported in part by a Grant for Research on Intractable Diseases from Ministry of Health, Labour, and Welfare of Japan 26070201.

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● 原　著 ●

妊娠糖尿病の新診断基準例の産褥早期予後とそのリスク因子

Early postpartum abnormal glucose tolerance in women diagnosed as having gestational diabetes by using the new IADPSG criteria

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受付日 2014年2月4日　採択日 2014年6月9日

【要約】〈目的〉妊娠糖尿病（GDM）既往女性の将来の糖尿病発症率は、
して、
褥早期 AGT は、
後については報告が少ない。今回、
常（AGT）の頻度とその関連因子の検討を行ったので報告する。〈方法〉新基準導入後の GDM 症例の産褥 6 ～ 8
週の 75g 経口糖
定義し、
断された GDM15
平均年齢は 32.7 歳、平均妊娠前 body
であった。産褥初回 OGTT は平均産褥 7.3 週に施行し、
褥 AGT であった。単変量ロジスティック回帰分析では、
および新旧の診断基準が産褥 AGT の関連因子であった。20
の予測変数を用いた多変量ロジスティック回帰モデルでは、FPG のみが産褥 AGT
FPG87
は新基準のみを満たした症例であった。〈結論〉新診断基準で診断された GDM の産褥早期 AGT の独立関連因子は、
GDM 診断時の FPG であった。産褥早期の AGT を見逃さないという観点から、新基準は旧基準

●キーワード：妊娠糖尿病、産褥耐糖能異常

はじめに

妊娠糖尿病（以下 GDM）既往女性が将来、高率に糖尿病を発症するというエビデンスは、近年のライフスタイルの変化を背景として、ますます重要なテーマとなっている。1978 年から 2008 年までの GDM 追跡報告をもとにした Bellamy らのメタ解析[1]では、GDM 既往女性の将来の糖尿病発症の相対リスクは 7.43 倍であると報告されている。この Bellamy らのレビューで取り上げられた 20 報告のうち 16 論文は追跡期間が 10 年以内の報告である。最近の韓国からある報告[2]では、分娩後 5 年間の糖尿病発症率は 41% にも達し、東アジア人においてもその重要性は同様である。

ところで、こうした報告で用いられている種々の GDM の従来の診断基準は、「GDM 既往女性は将来高

率に糖尿病を発症する」というエビデンスに裏打ちされたO'Sullivanの報告[3]を根拠としたものである。一方、2010年3月に発表されたIn
of Diabetes Study Group（I　[4]によるGDMの新しい国際標準は、2010年6月、わが国では世界に先駆けていち早く導入された[5]。このGDMの新しい国際標準診断基準は、旧来の糖尿病発症リスクではなく、周産期予後との関連をもとに策定した初めての診断基準である。したがって、新診断基準で診断されたGDMが、従来のGDMの概念同様に将来の糖尿病発症のリスクとなるかについてはほとんど報告がない。

そこで今回われわれは、新診断基準で診断されたGDM症例の産褥早期（6～8週）の耐糖能異常（abnormal glucose tolerance；以下AGTと略す）の発症頻度とそのリスク因子の検討を行ったので報告する。

対象と方法

新基準導入後の2010年7月以降にGDMと診断し、2012年8月までに産褥早期のフォローアップ検査として75g経口糖負荷試験（oral glucose tolerance test；以下OGTTと略す）を施行したGDM症例を対象とした。GDM症例には診断時に全例に血糖自己測定（self-monitoring of blood glucose;以下SMBGと略す）を施行し、食事療法のみでは目標血糖値に到達しないものはインスリン療法を導入した。妊娠中の血糖管理はインスリン療法まですべて産婦人科主治医が行った。なお、妊娠中に診断した明らかな糖尿病は対象から除外し、また分娩後にインスリン療法を継続した症例も、妊娠中に診断した明らかな糖尿病として対象から除外した。

すべての症例を対象に、産褥早期（産褥6～8週）に75gOGTTを施行した。OGTTは10時間以上の絶食の後、空腹時、糖負荷後30分、60分、120分に血糖値（静脈血漿値）およびimmunoreactive insulin (I
た。産褥AGTは日本糖尿病学会の境界型および糖尿病型と定義した[6]。

産褥早期AGTと母体背景因子およびGDM診断時のOGTT検査結果について関連を検討した。母体背景因子として、年齢、妊娠前BMI、初産・経産、GDM診断時妊娠週数、インスリン治療の有無を検討した。GDM診断時のOGTT検査結果として、各血糖値（PG）、HbA1c値、空腹時I
よび新旧の診断基準での分類の相違について検討した。IIは（30分IRI値—空腹時IRI値）/（30分PG値—空腹時PG値）で算出した。新旧の診断基準については、GDM診断時のOGTTの結果が、旧基準に該当する場合を「旧基準」、新基準のみに該当する場合を「新基準」とした。まず単変量ロジスティック回帰分析を用いて上記各因子と産褥早期AGTとの関連性を検討し、関連候補因子（$p < 0.10$）を抽出した。抽出された関連候補因子による多変量ロジスティック回帰モデルを用いて独立関連因子（$p < 0.05$）の抽出を行った。

結　果

対象期間に当科で管理したGDM症例は155例であった。妊娠中はGDMの診断基準を満たし、分娩後に継続してインスリン療法を必要とした症例は認めなかった。そのうち、産褥6～8週に75gOGTTを施行した症例は130例（フォローアップ率84%）で、以下の解析はこの130例を対象とした。対象GDM症例の母体背景とGDM診断時の検査結果を表1、周産期予後と産褥OGTT結果を表2に示した。産褥初回OGTTは平均産褥7.3週に施行した。90例（69.2%）は正常のOGTT結果であったが、糖尿病型5例（3.8%）および境界型35例（26.9%）の計40例（30.8%）が産褥AGTと判定された。産褥AGTの16例（40%）は新基準のみを満たした症例で、いずれも境界型であった。

産褥早期のOGTTの結果が正常型であったもの（正常群）と産褥AGT群との検査結果の比較を表3に示し、母体背景および診断時OGTT結果を比較した（表

表1　対象GDM症例の母体背景とGDM診断時の検査結果 (n=130)

	平均±SD　または　%
年齢（才）	32.7±5.4
妊娠前BMI	23.6 ± 4.9
初産婦（%）	63例（48%）
GDM診断週数	25.1±5.9
診断時HbA1c（%）(n=107)	5.1±0.4
診断時75gOGTT	
空腹時血糖値（mg／dl）	86±10
1時間血糖値（mg／dl）	181±28
2時間血糖値（mg／dl）	157±29
空腹時IRI（μU/ml）(n=78)	7.6±3.8
新基準のみGDM	69例（53%）
旧基準でもGDM	61例（47%）
診断時Insulinogenic index (n=77)	0.43±0.40
妊娠中のインスリン治療	74例（57%）

BMI: body mass index OGTT: oral glucose tolerance test
HbA1c、IRI、およびI.I.については測定症例数を別個に示した。

4-1、2)。母体背景では、妊娠前 BMI で有意に高値であった(p＝0.032)。年齢、初産婦の割合、診断時妊娠週数、インスリン治療の割合は差を認めなかった。診断時 OGTT 検査結果は、空腹時血糖値が産褥 AGT 群で有意に高く（p<0.002)、産褥 AGT 群では旧基準 GDM がより高頻度であった（p＝0.046)。

単変量ロジスティック回帰分析の結果を表５に示した。妊娠前 BMI、時間 PG、および新旧の診断基準が産褥 AGT の関連因子候補（p<0.10）として抽出された。これら５つの予測変数を用いた多変量ロジスティック回帰分析モデルでは、いずれの因子も有意な独立関連性を見いだせなかった。そこで、20％の測定欠損を含んだ HbA1c 値を除外し、残り４つの予測変数を用いた多変量ロジスティック回帰モデルとして検討したところ、FPG のみが産褥 AGT と有意な関連を認め（p=0.011)、妊娠前 BMI、関連を認めなかった。FPG と産褥 AGT の関連について ROC 曲線から得られたカットオフ値は 87 mg/dl で、FPG87 mg/dl 以上の場合、産褥 AGT 発症のオッズ比は 5.2（95% 信頼区間：2.1-13.9）であった。

表２　周産期予後と産褥 OGTT 結果

	平均 ± SD または %
分娩時妊娠週数	38.6±2.4 週
帝王切開（率）	34 例（26.2%）
出生体重（g）	2,942 ± 562 g
産褥初回 75gOGTT 施行週数	産褥　7.3±1.5 週
診断時 OGTT 血糖値　　空腹時（mg/dl）	89±10
1 時間値（mg/dl）	157±36
2 時間値(mg/dl)	135±83
HbA1 c 値（%）	5.1±0.3
産褥初回 OGTT 異常例	40 例　(30.8%)
IGT 型	35 例　(26.9%)
DM 型	5 例　(3.8%)

考　察

2010 年 3 月に IA 新国際標準診断基準[4] は 2010 年 6 月に日本でも承認され[5]、当院では 2010 年 7 月に本格的に導入した。今回、その導入後から 2012 年 8 月までの間に新診断基準によって診断し当科で治療的介入を行い、産褥早

表３　産褥 OGTT 正常群と AGT 群の産褥 OGTT 結果の比較

	正常(n=90)	AGT(n=40)	p 値
施行週数（産褥）	7.2±1.6	7.4±1.2	ns
HbA1c（%）	5.1±0.3	5.2±0.4	0.01
空腹時血糖値（mg／dl）	87±7	95±12	<0.001
1 時間血糖値（mg／dl）	144±30	188±30	ns
2 時間血糖値（mg／dl）	112±18	163±29	ns
空腹時 IRI（μU/ml）	4.4±2.8	6.9±5.1	<0.001
Insulinogenic index	0.59±0.51	0.40±0.25	0.03

表 4-1　産褥 OGTT 正常群 /AGT 群の比較（母体背景）

検討項目	産褥 75 g OGTT		p 値
	正常（n=90）	AGT(n=40)	
年齢（才）	33±6(21-45)	32±5(20-43)	ns
妊娠前 BMI	22.9±4.5 (16.2-35.7)	25.0±5.7 (17.2-39.2)	0.032
初産婦（%）	42(46.7%)	21(52.5%)	ns
GDM 診断週数	25±7(7-36)	24±6(12-35)	ns
インスリン治療あり	50(55.6%)	24(60.0%)	ns

表4-2　産褥OGTT正常群/AGT群の比較（診断時OGTT）

検討項目	産褥75gOGTT		p値
	正常(n=90)	AGT(n=40)	
診断時HbA1c（%）	5.1±0.3(4.4-5.8) (n=72)	5.3±0.5(4.3-5.9) (n=35)	
診断時OGTT			
空腹時血糖値(mg/dl)	86±10(69-105)	91±11(61-110)	0.002
1時間血糖値(mg/dl)	178±30(95-269)	189±20(144-219)	0.051
2時間血糖値(mg/dl)	157±26(90-206)	156±29(100-217)	ns
空腹時IRI(μU/ml)	6.5±3.0(1.9-13.9) (n=54)	7.9±5.0(1-18.6) (n=24)	ns
診断時I.I.	0.4±0.4(-0.3-1.86) (n=53)	0.4±0.3(0.1-1.6) (n=24)	ns
旧基準でもGDM	37(41.1%)	24(60.0%)	0.046

I.I.: Insulinogenic index
HbA1c、IRI、およびI.I.については測定症例数を別個に示した。

表5　産褥AGTの関連因子：単変量ロジスティック回帰分析

	χ^2値	p値
年齢	0.30	0.58
妊娠前BMI	4.59	0.032
初産・経産	0.38	0.57
GDM診断週数	0.45	0.50
診断時OGTT血糖値		
空腹時	9.91	0.0016
1時間値	3.69	0.055
2時間値	0.58	0.44
新旧診断基準	3.97	0.046
insulinogenic index	0.18	0.67
診断時HbA1c値	4.41	0.036
インスリン治療	0.23	0.63

期（6～8週）に達したGDM症例を対象とした。同期間のGDM診断症例は155例であった。そのうち、産褥早期（6～8週）に初回のフォローアップ検査として75gOGTTを施行した130例を対象に、産褥早期AGT発症頻度と、産褥早期AGTと関連する母体背景因子および妊娠中の診断時75gOGTT時の検査結果について検討した。

産褥早期AGT症例は40例（31%）に認められた。われわれは以前、新診断基準導入前の旧診断基準で診断されたGDM症例119例の産褥平均10カ月間フォローアップで、37.8%にAGTを認め、そのうち糖尿病型は9.2%であることを報告した[7]。今回は、新基準導入後のGDM症例について初めて検討し、産褥初回OGTTで30.8%にAGTを認め、そのうち3.8%は糖尿病型であった。フォローアップ期間の違いのため単純に比較はできないが、新基準導入後のGDM既往女性の産褥AGTの発症頻度は旧診断基準時代に匹敵するものであり、新基準で診断されるGDMにおいてもまた、GDM既往女性の産褥AGTの発症は決して低くなく、その産褥フォローアップの重要性が確認できた。今回の検討では、産褥初回AGTは、旧GDM診断基準に該当する「旧GDM群」で39%と高率であったが、新基準でのみ診断しうる「新GDM群」でも23%と4人に1人という高率であり、産褥早期AGT40症例のうち16例（40%）は新基準のみを満たすGDM症例であった。また多変量回帰モデルではその新旧の診断基準の差は有意な変数として残らなかった。多変量回帰モデルの結果はその統計的パワー不足の影響を否定できないものの、今回の結果は、新基準のみに該当する軽症例でもそのフォローアップが重要であることを示唆している。

多変量ロジスティック回帰モデルで産褥早期AGTと有意な独立関連性を認めた因子は、GDM診断時の空腹時血糖値のみであった。空腹時PG87mg/dl以上場合、産褥AGTのオッズ比は5.2（95%信頼区間：2.1-13.9）であった。Ekelundら[8]は、174例のGDM既往スウェーデン女性のフォローアップ研究で分娩後5年間の糖尿病発症因子を検討した。年齢、肥満度、および人種を補正した後、妊娠中のHbA1c値および空腹時PG値、1親等の糖尿病家族歴、および再発性GDMがDM発症リスク因子であり、HbA1c値5.7%（NGSP値）以上あるいは空腹時PG値5.2 mmol/L（93 mg/dl

告している。Jangらは、韓国におけるGDM既往女性の前向き追跡研究で、産褥5年以内に約40%の既往GDM女性が糖尿病に進展し、また糖尿病進展に関連する因子は診断時OGTTの空腹時血糖が最も有意な予測因子であることを報告している[2]。今回の検討ではHbA1c値については測定件数が少なく、独立性関連性の評価には至らなかったが、カットオフ値は異なるものの空腹時PGが独立関連因子である点は同様であっ

た。ただし、これらの報告はいずれもIA
以前の各国の種々の異なる診断基準を用いた報告であり、IA
プ研究はわれわれの知る限りいまだ報告がない。

われわれは以前、旧診断基準によるGDM既往女性168例を対象として同様の検討を行ったところ、産褥早期AGTの独立予測関連因子はIIと妊娠中のインスリン療法であった[9]。新診断基準によるGDM既往女性を対象とした今回の検討ではII、インスリン治療のいずれも有意な関連性を認めなかった。今回の検討は対象となる症例数が少ないこと、IIの測定症例数はさらに少ないこと、新基準による耐糖能異常の軽症化などが異なる結果の要因と思われ、さらに症例数を増やして再検討すべき課題である。

GDM既往女性が将来高率に糖尿病を発症するというエビデンスを確立した1978年のO'Sullivanの報告では、GDM既往女性の22～28年間のフォローアップ期間で、糖尿病発症率は38%に達するというものであった[1]。最近の報告では、産褥5年程度で30～40%が糖尿病を発症するとするものが多く[1,2,7]、日本人の追跡研究では、高島ら[10]はGDM既往女性の平均2.6年のフォローアップで42%、和栗ら[11]は平均5年間のフォローアップで40.8%が糖尿病を発症したと報告している。世界的な肥満と糖尿病のパンデミックと称される今日、GDM既往女性の分娩後のフォローアップは、GDM既往女性は糖尿病発症予防戦略、またGDM既往妊娠後の挙児希望女性における糖尿病合併妊娠に関連する先天奇形の予防戦略として、ますます重要な課題となっている。GDM既往女性における産褥早期AGTは、その後の糖尿病発症の最も鋭敏なリスク因子とされている[12]。したがって、産褥早期AGTと関連する妊娠中のリスク因子を特定することは、より効率的で見逃しの少ないフォローアップシステムを構築するうえで意義がある。

今回の結果は、新診断基準で診断されるGDM既往女性は、旧診断基準と同様に産褥AGTのリスクが高く、そのフォローアップが重要であることを示した。とくに空腹時PG値は、年齢、肥満度などの他のリスク因子の有無にかかわらず産褥早期AGTの有意な独立関連因子であり、妊娠中のGDM診断時の空腹時PG≧87 mg/dlを示した場合の産褥AGT発症補正オッズ比は5.2である。今回は133例という限られた統計的パワーでの解析であり、さらに症例数を増やして他の独立関連リスク因子を明らかにすることによって、効率的なフォローアップ体制の構築が可能となると思われる。

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● 総　説 ●

血糖自己測定法（SMBG）とリスク因子を用いた妊娠糖尿病への戦略的アプローチ

Risk triage algorithm : a new strategic approach to gestational diabetes

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はじめに

妊娠糖尿病（gestational diabetes mellitus, GDMと略す）の国際標準の新診断基準[1]が2010年にわが国に導入[2]されて3年が経過した。新基準の導入で、産婦人科医はもとより、糖尿病内科医にもその関心が高まり、GDMの臨床的意義を改めて問い直す良い契機となった。一方、新基準の導入によってGDMの頻度は2～3倍に増加し、臨床の現場では増加したGDM妊婦への対応に若干の混乱が生じている。本稿では、GDM妊婦の血糖管理について、その標準ツールとしての血糖自己測定法（self-monitoring of blood glucose, SMBGと略す）に加えて、「リスク因子トリアージ法」という新しい視点からのGDM管理法について提案したい。

GDMの血糖管理とSMBGの役割

SMBGの臨床応用の最初の報告は1978年の2つの論文[3,4]にさかのぼる。この最初の報告から1型糖尿病合併妊娠がSMBGの適応として紹介されている。このSMBGの導入によって、それまでは入院管理を余儀なくされていた1型糖尿病合併妊娠は外来管理が可能となり、その血糖管理は飛躍的に向上した[5]。1980年代に入ると、SMBGによる外来管理群と従来型の入院管理群を比較した無作為割付試験（RCT）[6]によってその有用性が確認され、SMBGはたちまち1型糖尿病合併妊娠の標準管理として、1型糖尿病合併妊婦の妊娠中の生活の質の改善に貢献した。その後すぐに2型糖尿病合併妊娠へも適応が拡大され、妊娠前糖尿病の血糖管理の標準ツールとして、周産期予後の改善に貢献した[7]。わが国においてもその有用性について大森[8]が詳細に報告している。

さらに1980年代後半にはGDMの血糖管理ツールとしての意義が検討され[9]、1990年代前半には、GDMにSMBGを導入することによって巨大児や新生児合併症の頻度を低下させ、耐糖能正常妊婦と同等の周産期予後の達成が可能となった。GDM症例でインスリン治療が必要な症例をSMBGによって適正に判定し、インスリン療法の導入率が上昇した効果と考えられる[10-12]。軽症の母体高血糖の血糖コントロール治療が周産期予後を改善するか、すなわち軽症GDMの治療的介入の意義について検討した初めてのRCTである豪州と米国の2つの大規模RCT[13,14]

SMBGが治療介入群のインスリン治療導入のための標準ツールとして設定された。このように、GDMにおけるSMBG導入は、食事療法のみでよいのか、あるいはインスリン治療の導入が必要なのかを判定するツールとしての意義が第一である。表1は、米国の各ガイドライン[15,16]におけるGDM診断時のインスリン導入判定のためのSMBGの実際である。米国では1日4検のSMBG測定を推奨している。われわれは空腹時および各食後の4検に就寝前（目標血糖値＜105mg/dl）を加えた1日5検のSMBGをGDM症例の標準SMBG法としている[17]。