Anti-islet autoantibodies in Japanese type 1 diabetes

Eiji Kawasaki, Katsumi Eguchi
Nagasaki University Hospital, Nagasaki, Japan

November 20-21, 2009 Cheju Island
Anti-islet autoantibodies in Japanese type 1 diabetes

1. Humoral autoimmune response to ZnT8
2. Type 1 diabetes and autoimmune thyroid disease (AITD)
3. Prediction of the disease progression in GADA⁺ NIDDM (LADA)
Anti-islet autoantibodies in Japanese type 1 diabetes

1. Humoral autoimmune response to ZnT8

2. Type 1 diabetes and autoimmune thyroid disease (AITD)

3. Prediction of the disease progression in GADA⁺ NIDDM (LADA)
Clinical subtypes of type 1 diabetes in Japan

Child-onset

- Fulminant: 10%
- Acute-onset: 90%
- Slow-onset: <1%

Adult-onset

- Fulminant: 6%
- Acute-onset: 67%
- Slow-onset: 27%

## Multiple causes of insulin-deficient diabetes

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genetic Abnormality</th>
<th>Extra-Pancreatic Disease Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1A diabetes</td>
<td>MHC and non-MHC genes</td>
<td>Organ-specific autoimmune disease</td>
</tr>
<tr>
<td>Type 1B diabetes</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>MODY-1</td>
<td>HNF-4α gene</td>
<td>No</td>
</tr>
<tr>
<td>MODY-3</td>
<td>HNF-1α gene</td>
<td>No</td>
</tr>
<tr>
<td>MODY-6</td>
<td>NeuroD1 gene</td>
<td>No</td>
</tr>
<tr>
<td>Wolfram Syndrome</td>
<td>WFS1 gene</td>
<td>Neuronal</td>
</tr>
<tr>
<td>Kearns-Sayre</td>
<td>mit DNA deletion</td>
<td>Neuronal</td>
</tr>
<tr>
<td>MELAS</td>
<td>mit DNA mutation</td>
<td>Hearing Loss</td>
</tr>
</tbody>
</table>

Anti-islet autoantibodies in type 1 diabetes

- GADA (1990)
- ZnT8A (2007)
- IA-2A (1994)
- IAA (1983)

ICA (Islet cell antibody) →
- GADA (Glutamic acid decarboxylase)
- IA-2A (Insulinoma-associated antigen-2)
- ZnT8A (Zinc transporter-8)
- IAA (Insulin autoantibody)

Diagnosis/Prediction
Zinc Transporter 8 (ZnT8)
Structure and functional role in beta cells

SLC30A8
R325W

SNP for type 2 diabetes

Insulin secretory granule

ZnT8

Insulin monomer

Zn^{2+}

Insulin hexamer

(E Kawasaki et al. Diabetologia 51:2299–2302, 2008)
ZnT8A in Japanese type 1 diabetes

Prevalence

- 58% (47/81)
- 0% (0/85)
- 21% (10/47)
- 2% (6/302)

ZnT8A index

- Acute-onset
- Fulminant
- GADA⁺ NIDDM
- GADA⁻ Type 2DM

Cut-off
Prevalence of ZnT8A associated with age-of-onset
(Acute-onset n=81)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10yrs</td>
<td>77%*</td>
</tr>
<tr>
<td>11~14yrs</td>
<td>51%</td>
</tr>
<tr>
<td>15~20yrs</td>
<td></td>
</tr>
<tr>
<td>&gt;20yrs</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05 vs. > 10yrs
Combinatorial analysis of anti-islet autoantibodies in acute-onset type 1 diabetes

(n=81, < 2wks after disease onset)

- GADA+ZnT8A: 3%
- IA-2A+IAA: 3%
- All negative: 9%

\[
\begin{align*}
\text{IA-2A} & \quad (65\%) \\
\text{ZnT8A} & \quad (58\%) \\
\text{GADA} & \quad (77\%)
\end{align*}
\]

\[
\begin{align*}
0\text{Ab} & \quad 10\% \rightarrow 9\% \\
\geq 1\text{Abs} & \quad 90\% \rightarrow 91\% \\
\geq 2\text{Abs} & \quad 73\% \rightarrow 79\%
\end{align*}
\]
Combinatorial analysis of anti-islet autoantibodies in fulminant type 1 diabetes

(n=85, < 2wks after disease onset)

GADA+ZnT8A 0%
IA-2A+IAA 0%
All negative 80%

Most Abs+ patients are single antibody-positive.
Anti-islet autoantibodies in Japanese type 1 diabetes

1. Humoral autoimmune response to ZnT8

2. Type 1 diabetes and autoimmune thyroid disease (AITD)

3. Prediction of the disease progression in GADA⁺ NIDDM (LADA)
Organ-specific autoimmune disease coexisting with type 1 diabetes in Japan

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mimura et al. # n</th>
<th>Our Cases n</th>
<th>Combined n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’ disease</td>
<td>26</td>
<td>23</td>
<td>49 (53.3)</td>
</tr>
<tr>
<td>Hashimoto's thyroiditis</td>
<td>15</td>
<td>17</td>
<td>32 (34.8)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>2</td>
<td>3</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>1</td>
<td>1</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>1</td>
<td>0</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Addison's disease</td>
<td>0</td>
<td>1</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>0</td>
<td>1</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Autoimmune uveitis</td>
<td>0</td>
<td>1</td>
<td>1 (1.1)</td>
</tr>
</tbody>
</table>

High titer and persistence of GADA in patients with type 1 diabetes and AITD

Type 1 diabetes with AITD

Type 1 diabetes without AITD

Negative

GADA epitope recognition in type 1 diabetic patients with and without AITD

<table>
<thead>
<tr>
<th></th>
<th>AITD (+) (n=23)</th>
<th>AITD (-) (n=23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1+E2</td>
<td>8 (35%)</td>
<td>19 (83%)</td>
<td>0.0012</td>
</tr>
<tr>
<td>N+E1+E2</td>
<td>11 (48%)</td>
<td>2 (9%)</td>
<td>0.0037</td>
</tr>
<tr>
<td>E1 only</td>
<td>2 (9%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>E2 only</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>E3 only</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>
GADA IgG isotype in type 1 diabetic patients with and without AITD

<table>
<thead>
<tr>
<th></th>
<th>AITD (+) (n=23)</th>
<th>AITD (-) (n=23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG1</td>
<td>23 (100%)</td>
<td>23 (100%)</td>
<td></td>
</tr>
<tr>
<td>IgG2</td>
<td>13 (57%)</td>
<td>2 (9%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>IgG3</td>
<td>12 (52%)</td>
<td>4 (18%)</td>
<td>0.014</td>
</tr>
<tr>
<td>IgG4</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
</tbody>
</table>
Anti-islet autoantibodies in Japanese type 1 diabetes

1. Humoral autoimmune response to ZnT8
2. Type 1 diabetes and autoimmune thyroid disease (AITD)
3. Prediction of the disease progression in GADA⁺ NIDDM (LADA)
Islet autoantibodies in Japanese patients initially diagnosed as type 2 diabetes

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Total (n=648)</th>
<th>Diet/OHA (n=357)</th>
<th>Insulin (n=291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GADA</td>
<td>31 (4.8%)</td>
<td>7 (2.0%)</td>
<td>24 (8.2%)</td>
</tr>
<tr>
<td>IA-2A</td>
<td>7 (1.1%)</td>
<td>1 (0.3%)</td>
<td>6 (2.1%)</td>
</tr>
<tr>
<td>IAA/IA</td>
<td>101 (15.6%)</td>
<td>12 (3.4%)</td>
<td>89 (30.6%)</td>
</tr>
</tbody>
</table>

GADA and/or IA-2A 34 (5.2%) 8 (2.2%) 25 (8.6%)

IAA, insulin autoantibodies; IA, insulin antibodies

To identify the predictive markers for disease progression in GADA$^+$ diabetes.....

Non-insulin treated type 2 diabetes
n=~3,000

GADA screening

GADA positive
n= 47

Follow up (~ 9yrs)

Started insulin therapy for glycemic control (n=17)

Treated by diet and/or OHA (n=30)
Proportion of GADA+ patients requiring insulin therapy classified according to the GADA titer

Low GADA (<20U/ml, n=17)

High GADA (≥20U/ml, n=30)

$P = 0.003$ (Log-rank test)
Proportion of GADA+ patients requiring insulin therapy classified according to the GADA epitope

Middle epitope (-) vs Middle epitope (+) vs Non-insulin treatment (%)

Follow up period (yrs)

Log-rank test $P = 0.002$
The frequencies of IA-2A, ZnT8A, and IAA in GADA⁺ NIDDM

GADA⁺ NIDDM (n=47)

- IAA⁺: 12 (26%)
- ZnT8A⁺: 9 (19%)
- IA-2A⁺: 7 (15%)

Multiple islet Abs: 17 (36%)

GADA single positive: 30 (64%)
Proportion of GADA\(^+\) patients requiring insulin therapy classified according to the simultaneous presence of other autoantibodies

\[ P=0.002 \text{ (log-rank test)} \]

GADA single positive

IAA/IA-2A/ZnT8A (+)
Risk factors for the progression of GADA\(^+\) NIDDM
Multivariate logistic regression analysis for the association of islet autoantibody status with early insulin requirement among GADA⁺ NIDDM

<table>
<thead>
<tr>
<th>Variable</th>
<th>Insulin requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>High GADA titer</td>
<td>0.61</td>
</tr>
<tr>
<td>Middle GADA epitope (+)</td>
<td>12.03</td>
</tr>
<tr>
<td>Multiple islet autoantibody (+)</td>
<td>13.77</td>
</tr>
</tbody>
</table>

All variables were entered simultaneously into the model.
High GADA titer, GADA≥ 20U/ml
Multiple islet autoantibody (+), positive for one or more of IAA, IA-2A, or ZnT8A
Collaborators

Nagasaki University
- Hirofumi Takino
- Norio Abiru
- Masakazu Kobayashi
- Tsuyoshi Soto
- Genpei Kuriya
- Kan Nakamura
- Shigenobu Nagataki (Emeritus professor)

Seitoku University
- Nobuo Matsuura

Tokyo Women’s Medical University School of Medicine
- Junnosuke Miura
- Yasuko Uchigata

Barbara Davis Center for Childhood Diabetes, USA
- John Hutton
Thank you for your attention!

World Diabetes Day

Spectacle Bridge, Nagasaki