Thyroid and Adrenal Autoimmunity

Jennifer M. Barker MD
Keystone Conference
Objectives

1. Describe the prevalence of thyroid autoimmunity and 21OH autoimmunity in patients with T1D
2. Describe the unique clinical presentation of Addison’s disease in patients with T1D
3. Describe the recommendations for screening for Thyroid disease and Addison’s disease in patients with T1D
4. Identify an appropriate follow-up plan for patients with T1D who are 21OH or thyroid autoantibody positive
Prevalence of autoantibodies

Diabetes Care 34:1211–1213, 2011
Figure 1—Frequency of nonislet, organ-specific autoantibodies is shown in 491 children with type 1 diabetes. Of these, 160 (32.6%) were positive for at least one nonislet, organ-specific autoantibody.
Prevalence of disease in patients with T1D vs. General Population

<table>
<thead>
<tr>
<th>Disease</th>
<th>T1D</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>8-15%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>0.5-1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Autoimmune Adrenal insufficiency</td>
<td>0.5-1%</td>
<td>0.01%</td>
</tr>
</tbody>
</table>
AUTOIMMUNE THYROID DISEASE
Thyroid Autoantibodies in T1D

### Thyroid Autoantibodies in T1D

#### Table 1 — Clinical and biochemical data in young patients with type 1 diabetes with or without positive thyroid antibodies (anti-TPO ≥100 units/ml or ≥1:100; anti-TG ≥100 units/ml or ≥1:100)

<table>
<thead>
<tr>
<th></th>
<th>Patients with at least one positive thyroid antibody</th>
<th>Patients without positive thyroid antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean ± SD or median (range)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1,530</td>
<td>13.6 ± 3.8*</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>1,530</td>
<td>8.4 ± 4.0*</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>1,530</td>
<td>5.2 ± 3.9*</td>
</tr>
<tr>
<td>Daily insulin dose (units/kg)</td>
<td>1,345</td>
<td>0.80 (0.0–2.6)</td>
</tr>
<tr>
<td>Height standard deviation score</td>
<td>1,530</td>
<td>−0.04 (−3.9 to 3.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1,530</td>
<td>19.9 (10.0–37.9)</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>1,511</td>
<td>8.1 (3.5–18.5)</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>1,371</td>
<td>3.34 (0.0–615.0)*</td>
</tr>
<tr>
<td>TSH &gt;3.5 µU/ml (%)</td>
<td>1,530</td>
<td>15.8*</td>
</tr>
<tr>
<td>Celiac disease (%)</td>
<td>1,530</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Data correspond to the most recent data set with positive thyroid antibodies in the DPV-Wiss database. *P < 0.001 compared with patients without positive thyroid antibodies.

---

Development of hypothyroidism with subclinical hypothyroidism

- def. normal T4 with elevated TSH

Incidence of Overt Hypothyroidism According to Different Risk Factors

JCEM 87:3221-3226
Longitudinal study of patients with T1D and TPO autoantibodies
ADRENAL AUTOIMMUNITY
Adrenal Autoantibodies

• Adrenal cortical auto-antibodies (ACA) associated with adrenal insufficiency
• 21-OH identified as an auto-antigen associated with autoimmune adrenal insufficiency
  ▪ Lancet 1992 339:1559-1562
• Found to be specific for adrenal insufficiency
  ▪ Absent in other autoimmune disease
• 21OH auto-antibodies tend to persist longer than ACA
• 60-85% of patients with “idiopathic AD” have positive 21-OH antibodies
Disease Model

- Stage 0: Local steroidogenesis suppresses adrenal antigen presentation within the adrenal cortex.
- Stage 1: Focal lymphocytic infiltration occurs.
- Stage 2: Area of lymphocytic infiltration expands.
- Stage 3: Systemic response targeted against adrenal antigens occurs.

- Antigen presentation: Progressive.
- Inflammatory infiltrate: Progressive.
- Local glucocorticoid concentrations: Decline.
- Phase of disease: Potential, Subclinical disease, Clinical disease.

Case MZ

- 15 year old female followed in Diabetes Autoimmunity Study in the Young
- HLA DR3/4
- No family history of diabetes
- Significant family history of thyroid disease
- 21-OH autoantibody positive at age 14.8 years
- Careful history shows some mild dizziness when going from a sitting to standing position, otherwise no symptoms of AD
- PE HR = 111 BP 124/80 BMI at the 8th percentile
  no noted increased pigment
21-OH autoantibody over time

21-OH Ab (index)

Age (years)
Case MZ

<table>
<thead>
<tr>
<th>Age</th>
<th>14.8 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>140 meq/L</td>
</tr>
<tr>
<td>K</td>
<td>4 meq/L</td>
</tr>
<tr>
<td>ACTH</td>
<td>75 pg/mL</td>
</tr>
<tr>
<td>Baseline cortisol</td>
<td>7 mcg/dL</td>
</tr>
<tr>
<td>Stimulated cortisol</td>
<td>13 mcg/dL</td>
</tr>
</tbody>
</table>

- Diagnosis of AD was made
- Treatment started with hydrocortisone, fludrocortisone
- Symptomatically improved
Case: FR

- CC: fatigue and easy bruising
- HPI: 13 year old female with
  - Bruising X 2 weeks
  - Fatigue X 2-4 weeks
  - Diffuse abdominal pain X 4-5 months - increasing
  - Weight loss (7-8 lbs)
- FH: MOC with hypothyroidism and vitiligo
- PE: skin with bruising/purpura T2 breast development; remainder normal
- Na = 121 mEq/L; glu = 412 mg/dL; Plt = 19

Hospital course
- Diagnosis of diabetes confirmed when high BG persisted
- Diagnosed with ITP
- Etiology of hyponatremia unclear
  - ? Chronic hyperglycemia
  - ? Renal losses
- Na = 126 mEq/L at d/c
- Platelets remained low
- Thyroid function normal
- Random cortisol of 23 ug/dL
Further follow-up

- **Na** = 135
- Continued muscle pain, fatigue
- Negative TPO
- Negative tTg
- Positive diabetes related antibodies (IAA, GAD, ZnT8)
- 21-OH antibody positive

### Hospital Evaluation

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (135-145 meq/L)</td>
<td>126</td>
</tr>
<tr>
<td>K (3.5-4.5)</td>
<td>3.8</td>
</tr>
<tr>
<td>Aldosterone (3-22 ng/dL)*</td>
<td></td>
</tr>
<tr>
<td>PRA (normal 50-30 ng/dL/hr)*</td>
<td></td>
</tr>
<tr>
<td>21-OH Ab (normal &lt;0.15)</td>
<td>1.5</td>
</tr>
<tr>
<td>ACTH</td>
<td>110</td>
</tr>
<tr>
<td>Baseline Cortisol</td>
<td>5</td>
</tr>
<tr>
<td>Stimulated Cortisol</td>
<td>11</td>
</tr>
</tbody>
</table>
• Diagnosed with AD
• Symptoms of fatigue and muscle cramping improved with treatment with fludrocortisone and hydrocortisone
• Has been followed for 4 years, with normal pubertal development, no evidence for celiac disease, thyroid disease or ovarian failure
Presentation of AD in population with T1D

- What is your experience?
Italian experience

<table>
<thead>
<tr>
<th>Total no.</th>
<th>ACA-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at start of follow-up (yr)</td>
<td>100</td>
</tr>
<tr>
<td>&lt;16</td>
<td>31.6 (range 4–72, median 31)</td>
</tr>
<tr>
<td>≥16</td>
<td>20</td>
</tr>
<tr>
<td>Males</td>
<td>80</td>
</tr>
<tr>
<td>Females</td>
<td>20</td>
</tr>
<tr>
<td>Autoimmune thyroid diseases and/or type 1 diabetes mellitus</td>
<td>74</td>
</tr>
<tr>
<td>Idiopathic hypoparathyroidism and/or candidiasis</td>
<td>17</td>
</tr>
<tr>
<td>Other autoimmune diseases</td>
<td>2</td>
</tr>
<tr>
<td>HCV-related hepatitis</td>
<td>5</td>
</tr>
<tr>
<td>First-degree relatives of autoimmune disease patients</td>
<td>2</td>
</tr>
</tbody>
</table>

At entry

100 Patients

70 Stage 0 (Normal adrenal function)

30 Impaired adrenal function

19 Stage 1

2 Stage 2

9 Stage 3

50 Stage 0

0 Stage 1

11 Stage 4 (AA)

4 Stage 0

6 Stage 1

9 Stage 4 (AAD)

2 Stage 4 (AAD)

9 Stage 4 (AAD)

The table below shows the factors related to progression to AD:

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>No. of enrolled patients</th>
<th>No. of patients developing AAD (%)</th>
<th>Univariate analysis HR (95% CI)</th>
<th>P</th>
<th>Multivariate analysis HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;16</td>
<td>20</td>
<td>14 (70.0)</td>
<td>5.02 (2.44–10.33)</td>
<td>&lt;0.001</td>
<td>1.47 (0.46–4.68)</td>
<td>0.52</td>
</tr>
<tr>
<td>≥16</td>
<td>80</td>
<td>17 (21.2)</td>
<td>1a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>10 (50.0)</td>
<td>3.02 (1.36–6.67)</td>
<td>0.01</td>
<td>3.37 (1.38–8.24)</td>
<td>0.01</td>
</tr>
<tr>
<td>Female</td>
<td>80</td>
<td>21 (26.2)</td>
<td>1a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired (stages 1–3)</td>
<td>30</td>
<td>20 (66.7)</td>
<td>6.10 (2.89–12.90)</td>
<td>&lt;0.001</td>
<td>6.15 (2.79–13.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal (stage 0)</td>
<td>70</td>
<td>11 (15.7)</td>
<td>1a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody titers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>38</td>
<td>16 (42.1)</td>
<td>1.98 (0.98–4.02)</td>
<td>0.06</td>
<td>3.33 (1.43–7.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low-medium</td>
<td>62</td>
<td>15 (24.2)</td>
<td>1a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coexisting diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical or potential APS type 1</td>
<td>17</td>
<td>14 (82.3)</td>
<td>5.07 (2.49–10.33)</td>
<td>&lt;0.001</td>
<td>5.23 (1.53–17.92)</td>
<td>0.01</td>
</tr>
<tr>
<td>Other conditions</td>
<td>83</td>
<td>17 (20.7)</td>
<td>1a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-DRB1 typing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRB1*03 and/or *04</td>
<td>39</td>
<td>13 (33.3)</td>
<td>0.96 (0.44–2.08)</td>
<td>0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other DRB1</td>
<td>40</td>
<td>13 (32.5)</td>
<td>1a</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* indicates significant difference.
Follow-up of 21-OH positive subjects followed at the BDC

20,518 serum samples screened (n = 12,782 individuals)

21OH-AA+ Individuals (n = 87)

Prospectively followed

21OH-AA+ progressors to Addison’s disease (n = 14)

Progressors with adrenal function testing prior to AD diagnosis (n = 7)

Discovered AD with adrenal function testing at AD diagnosis (n = 7)

21OH-AA+ Non-Progressors (n = 73)

Adrenal function testing (n = 54)

Clinical Endocrinology (2012), 76, 617–624
ACTH overtime in progressors vs. non-progressors
ROC curves for Biomarkers of AD

(a) 21OH-AA

- Area under the ROC curve:
  - Area: 0.8377
  - Standard error: 0.00449
  - 95% confidence interval: 0.7701 to 0.9053
  - P value: < 0.0001

(b) Renin

- Area under the ROC curve:
  - Area: 0.6787
  - Standard error: 0.09075
  - 95% confidence interval: 0.5007 to 0.8566
  - P value: 0.08380

(c) ACTH

- Area under the ROC curve:
  - Area: 0.9411
  - Standard error: 0.02712
  - 95% confidence interval: 0.8879 to 0.9943
  - P value: < 0.0001

(d) Peak cortisol (250, 60 min)

- Area under the ROC curve:
  - Area: 0.8158
  - Standard error: 0.06116
  - 95% confidence interval: 0.6586 to 0.9749
  - P value: 0.005287
Screening

• ADA (2013 Guidelines)
  ▪ Consider screening children with T1D for thyroid peroxidase and thyroid antibodies soon after diagnosis
  ▪ Measuring TSH concentrations soon after diagnosis of T1D, after metabolic control has been established, is reasonable. If normal, consider rechecking every 1-2 years, especially if the patient develops symptoms of thyroid dysfunction, thyromegaly or an abnormal growth rate

• ISPAD (2011 Guidelines)
  ▪ Screening for the most frequent associated autoimmune disorders i.e. thyroid dysfunction and celiac disease is strongly recommended even in apparently clinically healthy subjects with type 1 diabetes
  ▪ Every patient with diabetes should be screened at diagnosis and during follow-up for diabetic complications and associated conditions.
Follow-up of positive antibodies

• Thyroid
  ▪ Monitor growth and development
  ▪ Screen TSH and T4 levels every 6-12 months and with symptoms or poor linear growth

• Adrenal
  ▪ Monitor weight gain
  ▪ Monitor for symptoms
  ▪ Screen annually with ACTH level and consider further testing with cosyntropin stimulation testing if abnormal or significant symptoms