Auto-Antibodies as Predictors of Autoimmune Diseases

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Prospective studies have demonstrated that many autoantibodies can be detected in the serum of asymptomatic individuals who later develop an autoimmune disease. These antibodies can therefore precede the clinical symptoms of the disease by years, and could be used for prediction and possible prevention of autoimmune diseases.

Natural History of Autoimmune Diseases

- Genetic predisposition
- Triggering (environmental) factors
- Pathogenic immunological factors
- Precipitating events
- Specific auto-antibodies

- Normal functions
- Homeostatic mechanisms
- Abnormal functions

- Initial phase
- Sub-clinical phase
- Clinical phase
- Time
How Should a Positive Auto-Antibody, Found in an Asymptomatic Subject, Be Interpreted?

1. Are the Abs predictive of disease?
2. Are the Abs an epiphenomenon?
3. Are the results false positives?

Positive Predictive Value

\[
\text{Positive Predictive Value} \equiv \frac{\text{No. of Ab-positive subjects that develop the disease}}{\text{Total no. of Ab-positive subjects}} \times 100\%
\]

Predictive Value of Auto-Antibodies

Markers predictive of disease (diagnostic role)
1. in asymptomatic subjects
2. in subjects with few or with aspecific symptoms
3. in pregnancy

Markers predictive of disease course (prognostic role)
4. disease activity
5. disease severity
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Disease with Predictive Auto-Antibodies

1. Systemic lupus erythematosus
2. Sjogren's syndrome
3. Rheumatoid arthritis
4. Hashimoto's thyroiditis
5. Diabetes type 1
6. Celiac disease
7. Primary biliary cirrhosis
8. Addison's disease
9. Multiple sclerosis
10. Crohn's disease

Anti-dsDNA and SLE

Swaak T. and Smeenk R

Anti-Nuclear Antibodies and SLE


130 SLE subjects US Army → 115 (88%) Ab positive before diagnosis
130 controls → 5 (3%)
US army serum repository (sera stored up to 30 yrs)
Development of Autoantibodies Before the Clinical Onset of Systemic Lupus Erythematosus

The PPV ranged from:
95% for anti-dsDNA to 100% for anti-Sm

Mean value for all antibodies: 96%

Anti-Ro/La Abs and Sjögren's Syndrome

- 21 women (11 asymptomatic) anti-Ro positive with children affected with neonatal lupus and congenital heart block
- After 5 yrs, 8/11 (73%) developed a sicca syndrome
- 23 anti-Ro/La positive asymptomatic women with children with congenital heart block
- After 10 yrs, 11 were still asymptomatic 12 disease (3 SS, 3 SLE, 6 UCTD)
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Anti-CCP, RF and Rheumatoid Arthritis
The Mini-Finland Health Survey (1978-1980)

7,217 healthy adult subjects
Age and gender representative of the Finnish population
After 8 yrs → 21 RA

<table>
<thead>
<tr>
<th>Basal sample</th>
<th>After 4 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 RF +</td>
<td>21 RF +</td>
</tr>
<tr>
<td>6 RF -</td>
<td></td>
</tr>
</tbody>
</table>

Rheumatoid factors antedating clinical rheumatoid arthritis

Anti-CCP Before Symptom Onset

83 early RA patients, all were former blood donors serum samples available from bloodbank from up to 10 years before onset of first symptom

Specific Autoantibodies Precede the Symptoms of Rheumatoid Arthritis

79 blood donors with RA
Antibody onset
- CCP -14 yrs
- RF -11 yrs
- mean 4.5 yrs
- RF+ 9%
- CCP+ 21%
- RF and CCP+ 19%

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Specific Autoantibodies Precede the Symptoms of Rheumatoid Arthritis

<table>
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Specific Autoantibodies Precede the Symptoms of Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Table 1: Diagnostic value of IgM RF and anti-CCP for RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blind dose population 6.5 years before symptom onset</td>
</tr>
<tr>
<td>Sensitivity, Specificity, PPV, NPV, and prevalence</td>
</tr>
<tr>
<td>General</td>
</tr>
<tr>
<td>population</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>IgM RF</td>
</tr>
<tr>
<td>0.4</td>
</tr>
<tr>
<td>0.2</td>
</tr>
<tr>
<td>0.1</td>
</tr>
<tr>
<td>anti-CCP</td>
</tr>
<tr>
<td>0.4</td>
</tr>
<tr>
<td>0.2</td>
</tr>
<tr>
<td>0.1</td>
</tr>
</tbody>
</table>

Anti-Mitochondrial Antibodies and Primary Biliary Cirrhosis
Mitchison HC, et al., Hepatology 1996

Anti-Mitochondrial Antibodies and Primary Biliary Cirrhosis
Mitchison HC, et al., Hepatology 1996

<table>
<thead>
<tr>
<th>Histology</th>
</tr>
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<tbody>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Non-specific hepatitis</td>
</tr>
</tbody>
</table>

Histology
Positive
Negative
Non-specific hepatitis

The Newcastle Study (1972-1984)
29 pat. AMA pos ≥ 1:40
Asymptomatic and with a normal liver function (ALT, ALP, Bil)
(22 screening in population, 7 incidental finding)

The Northeast England Cohort
Prince MI, et al., Asymptomatic primary biliary cirrhosis: clinical features, prognosis, and symptom progression in a large population based cohort; Gut 2004; 53:865-70

770 patients with PBC
- definite (AMA + liver damage + histology)
- probable (AMA or liver damage)
301 symptomatic
469 asymptomatic
50% symptomatic after 5 yrs
95% symptomatic after 20 yrs

Survival after 25 yrs

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**Anti-Islet Cell Antibodies and Diabetes**
Bingley PJ, et al., *Diabetes Care* 1999
4,655 non-diabetics, 1st degree relatives of IDDM patients
ICA, GAD, IA2, anti-insulin
Follow up of 10 yrs
26 developed IDDM

**Progression to Diabetes vs. Number of Auto-Antibodies**
882 First-Degree Relatives of IDDM Patients (GAD, ICA512, Insulin)
Venge et al., *Diabetes* 1994; 43:106

**Gestational Diabetes: Risk at 2 Years**
Type 1 Diabetes by Autoantibodies ICA, GAD65, ICA512(IA-2) - 437 Women
Ziegler et al., *Diabetes* 1997; 46:969-67

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Prediction of Insulin-Dependent Diabetes Mellitus in Siblings of Children with Diabetes; A Population-Based Study

755 siblings of IDDM patients
32 developed IDDM within 8 yrs

<table>
<thead>
<tr>
<th>Antibody</th>
<th>PPV</th>
<th>Antibody</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>43%</td>
<td>0</td>
<td>0.8%</td>
</tr>
<tr>
<td>IA-2</td>
<td>55%</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>GAD</td>
<td>42%</td>
<td>2</td>
<td>25%</td>
</tr>
<tr>
<td>insulin</td>
<td>29%</td>
<td>3-4</td>
<td>70%</td>
</tr>
</tbody>
</table>

Successful Prospective Prediction of Type 1 Diabetes in Schoolchildren Through Multiple Defined Autoantibodies
LaGasse JM, et al., Diabetes Care 2002; 25:505-11

1505 scholars
ICA, GAD, IA2, insulin
IDDM after 8 yrs

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>6*</td>
</tr>
<tr>
<td>IA2</td>
<td>0</td>
</tr>
<tr>
<td>GAD</td>
<td>0</td>
</tr>
<tr>
<td>insulin</td>
<td>0*</td>
</tr>
</tbody>
</table>

* Sensitivity 50%  ** Specificity 100%

Diabetes Autoimmunity Study in the Young
General population cohort Sibling/offspring cohort

Follow-up
screened HLA = 2 [162 Ab positive] LA positive

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 false</td>
<td>50 transient</td>
</tr>
<tr>
<td>112 confirmed</td>
<td>62 persistent</td>
</tr>
</tbody>
</table>

Barker et al., Prediction of Autoantibody Presence to Type 1 Diabetes, DAISY Study, J Clin Endocrinol Metab 89:3896, 2004
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Auto-Antibodies as Predictors of Autoimmune Diseases

Adrenal Cortex Antibodies and Addison's Disease

284 healthy subjects
1 anti-adrenal Ab
After 20 months →
1045 patients with autoimmune disease
8 anti-adrenal Ab
after 20 months →

Anti-Adrenal Antibodies and Addison's Disease in Subjects with Autoimmune Diseases

Betterle C, et al., JCEM 1997
8,840 adults with autoimmune disease
48 Ab+ → follow-up 13 yrs → 24 Addison (50%)

Betterle C, et al., JCEM 1997
808 children (5-12 a) with autoimmune disease
14 Ab+ → follow-up 10 yrs → 10 Addison (71%)

Anti-Thyroid Antibodies and Hypothyroidism

The Wickham survey

<table>
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</thead>
<tbody>
<tr>
<td></td>
<td>(in 1974)</td>
<td>F</td>
</tr>
<tr>
<td>2,779 adults</td>
<td>TPO/Tg</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>TSH</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>TSH+TPO/Tg</td>
<td>173</td>
</tr>
</tbody>
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Anti-TPO Ab in Pregnancy Predictive of Post-Partum Thyroid Dysfunction (PPTD)

<table>
<thead>
<tr>
<th>Test</th>
<th>PPTD (no.)</th>
<th>SEP</th>
<th>SPP</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPO</td>
<td>308</td>
<td>100.0</td>
<td>62.0</td>
<td>48.0</td>
</tr>
</tbody>
</table>

(Premawardhana LDE, et al., Thyroid peroxidase antibodies in early pregnancy: utility for prediction of postpartum thyroid dysfunction and implications for screening. Thyroid 2006; 16: 28)

Anti-Tissue Transglutaminase Antibodies and Celiac Disease

1994: 3,654 students (7-16 yrs) for IDDM
2001: 56 tTG and/or EMA +
10 CD already diagnosed
10 didn’t accept biopsy
36 biopsy → 27 CD
(14 silent CD, 11 gastrointestinal symptoms, 1 dermatitis, 1 astenia)

Serological tests were positive on average 6 yrs before diagnosis

A Prospective Study of the Incidence of Childhood Celiac Disease
22,346 newborns (Denver, CO) studied for HLA DQ2/DQ8 386 found HLA positive, followed for 7 yrs by the tTG test; 40 tTG positive → 19 celiacs

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Anti-Myelin Antibodies and Multiple Sclerosis

103 patients with a first demyelinating event
Anti-myelin oligodendrocytic glycoprotein (MOG) and anti-myelin basic protein (MBP) antibodies

- 22 MOG and MBP positive
- 42 MOG positive
- 39 negative

8 yr follow-up
83% of MOG positive and 95% of MOG and MBP positive developed definite multiple sclerosis vs. 23% of MOG and MBP negative


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Anti-Saccharomyces Cerevisiae Antibodies and Crohn's Disease

Israeli army
- 32 subjects with Crohn's disease (17 ASCA+)
- 95 controls

ASCA+ before diagnosis 10/32 (31.3%)
(Stored sera) 10/17 (59% of the ASCA+)
0/95 controls

ASCA positive on average 38 months before diagnosis

Israelian army
ASCAs as predictors of inflammatory bowel disease. Gut 2003: 54: 1223-6

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**Concluding Remarks**

- Numerous autoantibodies can be detected many years before the appearance of the first symptoms and the clinical diagnosis.
- Their predictive value is high.
- The higher the number of positive antibodies, the higher the risk of developing an autoimmune disease.
- It is essential to use methods with high diagnostic specificity to minimize false positives.