Autoimmune Polyglandular Syndromes

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Presenter Disclosure

Andrea Steck

Disclosed no conflict of interest
Learning objectives

- Define Autoimmune Polyglandular Syndromes (APS)
- Distinguish the different Autoimmune Polyglandular Syndromes (APS–1, APS–2, IPEX)
- Differentiate APS–1 from APS–2
- Identify IPEX
- Evaluate treatment options
Case presentation

- **HPI:** 34d male presents with FTT. BW was 6#1oz. At 2 wk old, weight was 7#. At 1mo, wt down to 6#14oz. Breastfeeding, but frequent emesis. Diagnosed with otitis media and started on Amox PO. After antibiotics started, increased stool output 10–20/day. Wt then (3d later) 6#1oz.
- **ROS:** +wt loss, no fever, no URI sx, +polyuria
History (continued)

- **PMH:** 38wk born to a G4P1 mom, +prenatal care, +oligo that resolved
- **FHx:**
  - Mother had fetal loss x3 (one due to hydrops)
  - Mat. aunt with multiple fetal losses and one male offspring died <1yr age from sepsis while being treated for nephrotic syndrome
<table>
<thead>
<tr>
<th>CHEMISTRY, BLD GRP</th>
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</thead>
<tbody>
<tr>
<td>NA/Sodium</td>
<td>135 *</td>
</tr>
<tr>
<td>NA/Sodium Blood</td>
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</tr>
<tr>
<td>NA/Sodium (Whole Blood)</td>
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</tr>
<tr>
<td>K/Potassium</td>
<td>5.5 *</td>
</tr>
<tr>
<td>K Blood</td>
<td></td>
</tr>
<tr>
<td>K (Whole Blood)</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>109 *</td>
</tr>
<tr>
<td>Bicarb/HCO3,S</td>
<td>13 *</td>
</tr>
<tr>
<td>BUN</td>
<td>12 *</td>
</tr>
<tr>
<td>Creatinine,S</td>
<td>0.23 *</td>
</tr>
<tr>
<td>Glucose,S</td>
<td>549 *</td>
</tr>
<tr>
<td>Glucose,S - OL</td>
<td></td>
</tr>
<tr>
<td>Glucose (Glucometer)</td>
<td>514 *</td>
</tr>
<tr>
<td>Glucose Whole Blood</td>
<td></td>
</tr>
<tr>
<td>GLUCOSE (WHOLE BLOOD)</td>
<td></td>
</tr>
<tr>
<td>A1C Hemoglobin</td>
<td>4.3</td>
</tr>
<tr>
<td>A1C Hemoglobin - OL</td>
<td></td>
</tr>
<tr>
<td>Calcium,S</td>
<td>9.5 *</td>
</tr>
<tr>
<td>Ionized Calcium</td>
<td></td>
</tr>
<tr>
<td>IONIZED CALCIUM (WHOLE BLOOD)</td>
<td></td>
</tr>
<tr>
<td>Total Protein,S</td>
<td>5.9 *</td>
</tr>
<tr>
<td>Albumin,S</td>
<td>3.0 *</td>
</tr>
</tbody>
</table>
Further testing

- Antibodies:
  - GAD65 Ab: 1284 U (strongly positive, nl <20)
  - Insulin Ab: 0.023 (positive, nl <0.01)
  - IA-2 and ZnT8RW Ab: negative
- IgE 2911 (nl 0–29)
- Biopsy: Small intestines with significant inflammation (lymphocytes, macrophages, neutrophils), epithelial apoptosis, severe loss of architecture (crypt and villous loss); sigmoid histology with similar loss of architecture and severe inflammation
- Genetic testing: Novel substitution in FOXP3 which affects the last nucleotide in exon 9 and may either cause aberrant splicing or a missense change
Treatment

- 6/2– Admit for FTT
- 6/3– hyperglycemic → Initially on insulin gtt then transitioned to Lantus
- Difficulty maintaining BGs with SQ so back to Insulin gtt
- 6/10– Started on Tacrolimus
- 8/3– Pump attempted, quickly back to insulin gtt
- 9/8– Transferred for HSCT
- 10/14– HSCT
- Diabetes described as “brittle” requiring insulin gtt with frequent adjustments
- At 9 months– Pump started
- 19 months: Slow Tacrolimus taper (4 month taper)
- 23 months: insulin stopped, nl BG (occ. BG in 150’s)
Outline

- Define APS
- Distinguish the different APS (APS–1, APS–2, IPEX)
- Pathogenesis & characteristics of APS–1
- Pathogenesis & characteristics of APS–2
- Pathogenesis & characteristics of IPEX
- Treatment options
Autoimmune Polyglandular Syndromes

- Characterized by the presence of multiple autoimmune disorders and, in some cases, immunodeficiency
- Include monogenic disorders such as APS-1 and IPEX, as well as complex genetic disorders such as APS-2
- Also known as:
  - APECED syndrome (APS-1)
  - Schmidt syndrome (APS-2)
  - Carpenter’s syndrome (APS-2)
APS: Common phenotype

**APS–1:**
- Mucocutaneous candidiasis
- Hypoparathyroidism
- Addison’s disease

**APS–2:**
- Addison’s disease
- Autoimmune thyroid disease
- Type 1 diabetes

* APECED – autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy
APS–1: Pathogenesis

- Monogenic disorder which results from a mutation in AIRE (AutoImmune REgulator) gene
- Central tolerance to self-antigens is lost, inducing autoimmune disorders as autoreactive T cells escape into the periphery
- More than 40 mutations described, most are autosomal recessive
- Almost all patients have autoantibodies to interferon–omega and INF–a (DD: thymoma associated with myasthenia gravis)
- Rare, more common in certain European populations (Finns, Sardinians and Iranian Jews)
- Occurs in childhood or adolescence

Husebye & al, Immunity 2010
**APS–1: clinical characteristics**

Must have 2 of the 3 components (typically occur in this order):

- 1) Mucocutaneous candidiasis
- 2) Hypoparathyroidism
- 3) Addison’s disease

May also have:

- Type 1 diabetes
- Hashimoto’s thyroiditis
- Autoimmune hepatitis
- Hypergonadotrophic hypogonadism
- Chronic atrophic gastritis/ Pernicious anemia
- Alopecia
- Vitiligo

Proust-Lemoine & al, Presse Med 2012
Mucocutaneous candidiasis is the first sign in 75–93% of cases
Followed by hypoparathyroidism with peak incidence between 5–6 years, then by Addison’s disease by age 13
Classic criteria (2 out of 3) found in 22% by 5 years, 67% by 10y, 89% by 20y and 93% by 30y
Ectodermal manifestations include vitiligo, alopecia, keratoconjunctivitis, dental enamel hypoplasia, pitted nail dystrophy

Perheentupa, Endocrinol Metab Clin N Am 2002
Prevalence of different manifestations in APS1 Sardinian patients

Meloni & al, JCEM 2012
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>APS–1</th>
<th>APS–2</th>
<th>IPEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>Rare</td>
<td>Common</td>
<td>Very rare</td>
</tr>
<tr>
<td>Incidence</td>
<td>&lt;1:100,000/year</td>
<td>1–2:10,000/year</td>
<td></td>
</tr>
<tr>
<td>M/F ratio</td>
<td>About 1:1</td>
<td>1:3</td>
<td>Only males</td>
</tr>
<tr>
<td>Onset</td>
<td>Infancy</td>
<td>Adulthood</td>
<td>Infancy</td>
</tr>
<tr>
<td>Relatives at risk</td>
<td>Siblings</td>
<td>Multiple generations</td>
<td>None</td>
</tr>
<tr>
<td>Genetics</td>
<td>AIRE mutations Autosomal recessive</td>
<td>Polygenic HLA–DR3, DR4 Non–HLA genes</td>
<td>FOXP3 mutations X–linked</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Aspleniaism Mucocutaneous candidiasis</td>
<td>None</td>
<td>Immune dysregulation</td>
</tr>
<tr>
<td>Type 1A diabetes</td>
<td>20%</td>
<td>20–50%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>100% interferon omega Ab</td>
<td>21–OH, TPO, Tg, insulin, IA–2, GAD, ZnT8, TTG, other</td>
<td>Present depending on disease manifestation</td>
</tr>
</tbody>
</table>

Michels & Gottlieb, Nat.Rev.Endocrinol 2010  
Kahaly, European Journal of Endocrinology 2009
APS–2: Pathogenesis

- Complex genetic disorder
- Highest risk genotype is HLA DR3/4
- Contribution of non–HLA genes (MICA 5.1, PTPN22, INS, CTLA–4)
- Occurs in adults with female to male ratio 3:1
- Prevalence 1/20,000

Michels & Eisenbarth, J Intern Med 2009
APS–2: clinical characteristics

Must have Addison’s disease

- Must have 1 of the following:
  - Autoimmune thyroid disease
  - Type 1 diabetes

Schmidt syndrome: Addison & AIT
Carpenter’s syndrome: Addison and T1D

May also have:

- Hypergonadotrophic hypogonadism
- Pernicious anemia
- Celiac disease
- Alopecia
- Vitiligo
- Myasthenia gravis
- Autoimmune hepatitis
By definition, Addison’s disease is present in 100% cases
ALT occurs in 70–90% and T1D in 20–50%
Only about 10% have the complete triad
90% of new onset patients with Addison’s disease have positive 21–OH Ab
About 30% subjects with positive 21–OH Ab progress to adrenal failure over 6 years

Owen & al, Endocrinol Metab Clin N Am 2009
Stages in the development of Addison’s disease

Eisenbarth, NEJM 2004
## Autoantigens and corresponding diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Autoantigen</th>
<th>Tissue/cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves disease</td>
<td>TSH receptor</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>TPO, Tg</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Calcium-sensing receptor</td>
<td>Parathyroid</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>GAD, IA–2, IAA, ZnT8</td>
<td>Endocrine pancreas</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>21–OH, 17–OH, P450scc</td>
<td>Adrenocortical</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>17–OH, CYP450scc</td>
<td>Ovarian/testicular</td>
</tr>
<tr>
<td>Autoimmune gastritis</td>
<td>H,K–ATPase</td>
<td>Gastric mucosa</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Intrinsic factor</td>
<td>Gastric mucosa</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>TTG IgA</td>
<td>Small intestine</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>Tyrosinase</td>
<td>Melanocytes</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Tyrosine hydroxylase</td>
<td>Hair follicles</td>
</tr>
</tbody>
</table>

scc: side-chain cleavage enzyme

Kahaly, Presse Med 2012
Kahaly, European Journal of Endocrinology 2009
IPEX

- Immune dysregulation
- Polyendocrinopathy
- Enteropathy
- X-linked

Barzaghi, Frontiers in Immunology 2012
Rubio-Cabezas, Diabetes Care, 2009
Pathogenesis

- Mutations in the transcription factor forkhead box p3 (FOXP3)
  - Loss of function mutations
  - More than 60 mutations described
- FOXP3 gene maps to chr. X (Xq11.23) and encodes a protein of 431 amino acids
  - Master gene of Treg cells
- FOXP3 is a critical regulator of CD4+CD25+ T cell development and function

Quiros, Allergol Immunopathol 2009
The clinical manifestations of IPEX are due to immune dysregulation.

This leads to autoimmune disease and allergic inflammation:

- Histology demonstrates lymphocytic infiltrates with or without associated autoantibodies.
- Allergic inflammation manifests as eczema, food allergies, eosinophilia, and elevated total and antigen specific IgE.
- These factors interact – a response to an allergen can then cause increased autoimmune disease.
Hyperglycemia or glucose intolerance may be present from birth.

Diagnosis of TIDM usually within the first year of life:
  - Anti-islet cell Ab may or may not be present
  - Lymphocytic infiltration/destruction of pancreas

Hypothyroidism (rarely hyperthyroidism)

Rarely GH deficiency or adrenal insufficiency may be present.
Intractable Diarrhea: watery, mucoid, bloody
- May begin while breastfeeding and thus is independent from cow milk or gluten introduction
- Worse by switching to formula
- Persists despite dietary exclusions and bowel rest

Vomiting

Gastritis

Ileus

Colitis

Autoimmune hepatitis is frequently seen in conjunction with autoimmune enteropathy
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- Pathogenesis & characteristics of IPEX
- Treatment options
Treatment of APS–1

- Treatment of candidiasis
  - Topical or systemic antifungals
- Treatment of hypoparathyroidism
  - Calcium and calcitriol
  - Goal: Ca in lower half or slightly below normal range (avoid high urinary Ca concentration)
- Treatment of adrenal insufficiency
  - Glucocorticoid and mineralocorticoid replacement
- Treat other components if present
- If asplenism, vaccinations against S. pneumoniae, N. meningitides and H. influenzae
- Increased mortality at 10–20%

Husebye, Journal of Internal Medicine 2009
Recommendations

- High clinical suspicion of other autoimmune disease needs to be maintained
- Evaluate patients every 6 months and screen for antibodies
- If antibodies present without associated disease, perform functional testing
- Patients with 21-OH Ab should be tested annually (ACTH stim. test) unless symptoms
Treatment of APS–2

- Hormone replacement
- Patient with Addison’s disease have a 50% lifetime risk of developing an additional autoimmune disease
- Recommend wearing an ID bracelet
- Thyroid hormone replacement in undiagnosed Addison’s disease may precipitate adrenal crisis (as thyroid hormone increases hepatic clearance of cortisol)
- Psychosocial support
Treatment of IPEX

- Recommendations are based on case reports
- Supportive care with fluid resuscitation, TPN, insulin, antimicrobials, blood products
- Immune suppression weighed against infection risk
- Glucocorticoids are first line therapy to limit progression of organ
- Cyclosporine and/or tacrolimus have been most commonly used in conjunction with steroids

Baud, NEJM 2001
Hematopoietic Stem Cell Transplantation

- Early HSCT leads to the best outcome, as the organs are not yet damaged from autoimmunity and the adverse effects of therapy
- 28 cases of HSCT have been reported in the literature and 6 have died
- Longest follow up is 8 years post transplant
- Both myeloablative and non–myeloablative conditioning regimens were used in order to limit complications associated with transplantation
Thank you