

**Autoimmune Endocrine Disorders:
Who and How to Evaluate
A Case Based Discussion**

Jennifer M. Barker MD
Pediatric Endocrinology
Children's Hospital Colorado
University of Colorado Anschutz Medical Campus

Objectives

- **Describe the screening guidelines for autoimmune endocrine disorders in:**
 - Type 1 diabetes
 - Down syndrome
 - Turner syndrome
- **Discuss laboratory evaluation for autoimmune endocrine disorders**
- **Identify clues in the history and physical examination that would lead to further testing for autoimmune endocrine disorders.**

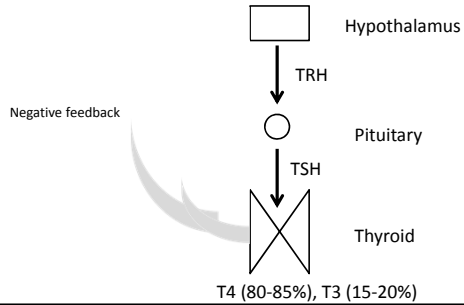
Outline

- Brief overview of the autoimmune disorders
- Overview of autoimmune endocrine diseases in:
 - Type 1 diabetes
 - Down syndrome
 - Turner syndrome
- Case discussion
- Summary

BRIEF OVERVIEW OF AUTOIMMUNE DISORDERS

Thyroid disease

Hypothalamic/pituitary/thyroid axis



Hypothyroidism

- Symptoms
 - Decreased linear growth velocity
 - Many others!
- Physical examination
 - Goiter
 - Decreased relaxation phase of reflexes
 - Sallow complexion
 - Round face
- Laboratory evaluation
 - Low TT4, TT3
 - Elevated TSH
 - Autoantibodies:
 - anti-thyroid peroxidase (TPO)
 - anti-thyroglobulin (TG)

Hyperthyroidism

- Symptoms
 - Weight loss, heat intolerance, palpitations, etc.
 - Can be difficult to assess in a patient with developmental disability (Down syndrome)
 - But you have to ask!
- Physical examination
 - Increased heart rate and blood pressure
 - Hyperdynamic precordium
 - Increased reflexes
- Laboratory evaluation
 - Elevated TT4, TT3, FreeT4
 - Suppressed TSH (less than 0.01)
 - Autoantibodies:
 - Thyroid stimulating immunoglobulin (TSI)
 - Thyroid receptor antibody (TRab)

Celiac Disease (CD)

- Enteropathy
- Triggered by ingestion of gluten in a susceptible individual
- Leads to malabsorption and growth failure in children
- Excellent review of Celiac Disease: Fasano A, Catassi C. N Engl J Med 2012;367:2419-2426

Epidemiology of celiac disease

- 0.6-1% of the population has celiac disease
- 20% of those with disease are diagnosed
- Increased in:
 - Type 1 diabetes (3-16%)
 - Hashimoto's thyroiditis (5%)
 - Down syndrome (5%)
 - Turner syndrome (3%)
 - IgA deficiency (9%)
 - Those with a first degree relative with CD (10-15%)

Clinical Presentation of celiac disease

- Classic –
 - diarrhea
 - malnutrition
 - failure to thrive
- Atypical –
 - poor growth, delayed puberty
 - evidence for malnutrition
 - neurologic and psychiatric abnormalities
- Physical examination
 - May be normal
 - Can have specific rashes
 - Dermatitis Herpetiformis - severe, itchy, blistering skin rash
 - 15-25% of people with celiac disease will have it

Testing for Celiac Disease

- Tissue transglutaminase (IgA)
 - 95% sensitive and specific
 - First line screening test
 - Get with **IgA** level to rule out IgA deficiency
- Antiendomysial antibodies (IgA)
 - 90% sensitive, 98% specific
 - Useful with an uncertain diagnosis
- Deamidated gliadin peptides (IgG)
 - IgA deficiency and young children
- Tissue transglutaminase (IgG)
 - IgA deficiency
- HLA-DQ2 or HLA-DQ 8 (genetic testing)
 - High negative predictive value

Diagnosis of celiac disease

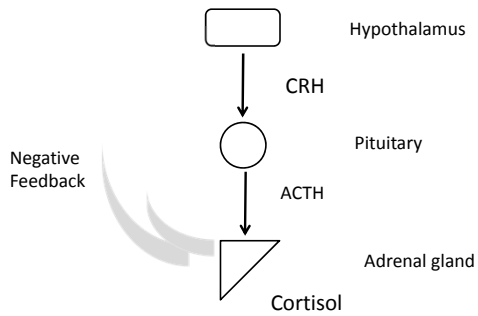
- High index of clinical suspicion
- Screening labs may indicate malabsorption
 - Anemia
 - Vitamin D deficiency
- Antibody screen
- Confirmatory small intestinal biopsy
- Improvement in antibody levels and biopsy on gluten free diet

Addison Disease (AD)

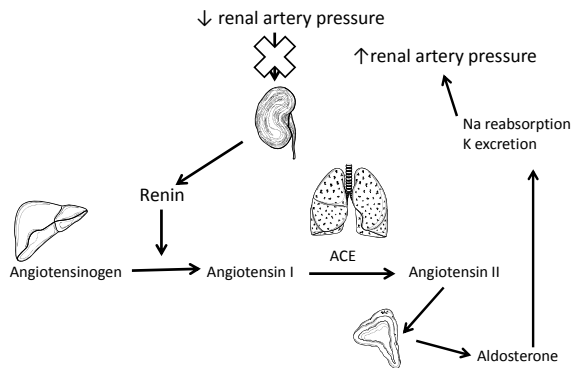
- Autoimmune endocrine disease resulting in primary adrenal insufficiency with low cortisol and aldosterone levels
- Rare: Prevalence 0.5-1/10,000
- Clinical practice guidelines:
 - J Clin Endocrinol Metab 2016, 101(2):364–389

Adrenal physiology

- Review of hypothalamic/pituitary/adrenal axis



Renin-Angiotensin-Aldosterone



Clinical Presentation of AD

- Non-specific symptoms:
 - fatigue, weight loss, nausea, pre-syncope, syncope
- Increased pigment
- Salt craving
- PE with orthostatic hypotension, increased pigment

Note: symptoms may exist for years before the diagnosis is considered

AD diagnosis

- Abnormalities of electrolytes:
 - Hyponatremia
 - Hyperkalemia
 - Acidosis
- Elevated ACTH and PRA
- Positive 21-OH antibody
- May require high dose ACTH stimulation testing to diagnose:
 - Expect cortisol level 60 minutes after cosyntropin to be greater than 18-20 mcg/dL

TYPE 1 DIABETES

Type 1 diabetes (T1D)

- T1D is an autoimmune disease resulting in destruction of the pancreatic β - cells
- T1D is associated with:
 - Autoimmune thyroid disease
 - Hypothyroidism > Graves disease
 - Celiac disease
 - Addison's disease
 - Other?

Thyroid disease and T1D

- \approx 20-30% will have + TPO/TG antibodies
- \uparrow in females vs. males
- \uparrow by age and diabetes duration
- Risk for thyroid disease in those with + antibodies \uparrow overtime
 - 80% with + antibodies have hypothyroidism after 20 years of follow-up

Screening for thyroid disease in T1D

- ADA (2016 Guidelines)
 - Consider screening for TPO and TG antibodies (at diagnosis)
 - Measuring TSH concentrations soon after diagnosis of T1D, after metabolic control has been established, is reasonable.
 - Consider rechecking TSH every 1-2 years.
 - Monitor for and screen TSH with:
 - symptoms of thyroid dysfunction,
 - thyromegaly
 - abnormal growth rate
- ISPAD (2014 Guidelines)
 - Screen TSH and TPO or TG antibodies at diagnosis
 - Monitor TSH every 2 year in antibodies negative patients
 - Monitor TSH more frequently (? How much more frequently) in antibody positive patients

Celiac disease and T1D

- Overlapping genetic risk
 - HLA DQ2/DQ8
- Multiple populations with T1D screened with TTg antibody – show prevalence of 3-16% positive
 - Biopsy positive in approximately 50-75% of those biopsied
 - Many of those positive are asymptomatic
- Most cases are identified within the first 5 years of diagnosis of T1D
- Risk has been related to ↓ age of onset of diabetes

Celiac disease and T1D

- Children identified by screening are often asymptomatic
- No increased risk for severe hypoglycemia or DKA
- Patients with T1D and CD ↑ risk for thyroid disease
 - Diabetes Care. 2016 Mar;39(3):371-5
- CD and T1D is associated with ↓ BMD but no ↑ in fracture rate
 - J Pediatr. 2016 Feb;169:44-48
 - J Pediatr. 2016 Feb;169:49-54
- Treatment adds financial and logistical burden to families already burdened with diabetes management

T1D and celiac disease – recommendations for screening

- ADA (2016 guidelines)
 - “Consider” screening TTg, IgA and/or deaminated gliadin antibodies at diagnosis
 - “Consider screening in children who have a first-degree relative with celiac disease, growth failure, weight loss, failure to gain weight, diarrhea, flatulence, abdominal pain, or signs of malabsorption or in children with frequent unexplained hypoglycemia or deterioration in glycemic control”
- ISPAD (2014 guidelines)
 - Screen at diagnosis with TTg or EMA and IgA
 - Screen every 1-2 years
 - Screen sooner with symptoms, growth concerns, glycemic variability

Addison's disease and T1D

- 0.5-1% of patients with T1D have AD
- 1.5-2% of patients with T1D have positive 21-OH antibodies
- Patients with diabetes with AD can present with symptoms of decreased insulin dose, decreased hemoglobin A1c, increased hypoglycemia
- No recommended routine screening

DOWN SYNDROME

Down syndrome and thyroid disease

- Congenital hypothyroidism 1–7%
- Acquired primary hypothyroidism 0.3–3%
- Subclinical hypothyroidism 12.5–33%
- Hyperthyroidism up to 2%
- ↑ risk for acquired primary hypothyroidism with + TPO antibodies

Recommendations for screening thyroid function in DS

- AAP guidelines (2011)
 - Newborn screen for thyroid function
 - Measure TSH at 6 months, 12 months and then annually

Down syndrome and celiac disease

- Risk for celiac disease in patients with Down syndrome 5-10% across multiple populations
- No difference noted in HLA predisposition in patients with celiac disease and Down syndrome compared with patients with celiac disease and no Down syndrome
- Symptoms may be difficult to assess

Down syndrome and celiac disease screening recommendations

- AAP guidelines (2011)
 - Screen for symptoms
 - Check TTg with symptoms
- North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
 - At age 3 or after at least 1 year of gluten exposure
 - Repeat screening at some interval

TURNER SYNDROME

Turner syndrome and thyroid disease

- Primary hypothyroidism 20%
 - Can be diagnosed as a young child
- Graves disease 1-2%
- ↑ risk of overt hypothyroidism with + TPO antibodies in those with subclinical hypothyroidism

Recommendations for screening for thyroid disease in TS

- Turner syndrome consensus study group (2007)
 - Screen all girls with TSH, T4 annually starting at age 4 years
- Guidelines are consistent across groups

Turner syndrome and celiac disease

- Girls and women with Turner syndrome have a known increase in hypothyroidism
- Risk for celiac disease 2-5% across different populations
- Commonly diagnosed when adult women with TS re-present as adults for comprehensive care
- Similar HLA predisposition in the population with TS

Recommendations for screening

- Turner syndrome consensus study group
 - At diagnosis (> age 4 years)
 - Screen with TTg
 - Repeat screening for symptoms of celiac disease and every 2-5 years
- North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
 - Screen at diagnosis, if diagnosis is at age 3 or after at least 1 year of gluten exposure
 - Repeat screening at some interval

BONUS: THYROID AND CELIAC

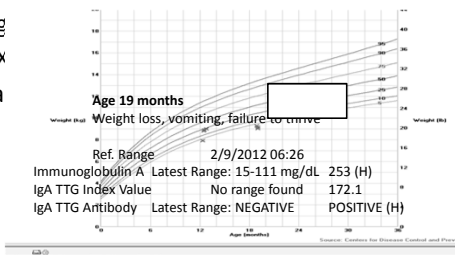
Autoimmune thyroid disease and celiac disease

- Overlapping genetic risk
 - DQ2
- Risk for celiac disease is increased in patients with both hypo and hyperthyroidism
- Patients with celiac disease are at an increased risk for autoimmune thyroid disease
- Patients with celiac disease and hypothyroidism have increased requirements for thyroid hormone replacement which improved with GFD
- Risk ranges from 2-5%

CASES

Patient with type 1 diabetes

- Ag
- Dx
- La



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)

FR continued

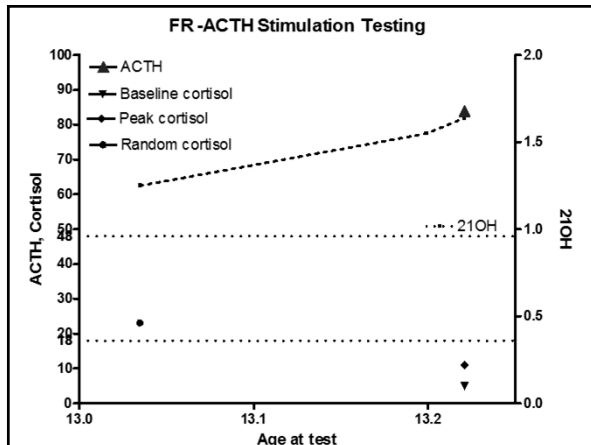
- PMH: seasonal allergies; MCL tear
- FH: MOC with hypothyroidism and vitiligo
- PE: skin with bruising/purpura (not noted to be hyperpigmented); T2 breast development; remainder normal

Laboratory evaluation

- Day PTA Na = 121 mEq/L; glu = 412 mg/dL; Plt = 19
- ED: Na = 124 mEq/L; glu = 364 mg/dL; Plt = 11
- Hospital course
 - Diagnosis of diabetes confirmed when high BG persisted
 - Etiology of hyponatremia unclear
 - ? Chronic hyperglycemia
 - ? Renal losses
 - Na remained low (at 126 mEq/L) at d/c
 - Platelets remained low
 - Thyroid function normal
- What else do you want to know?

Further follow-up

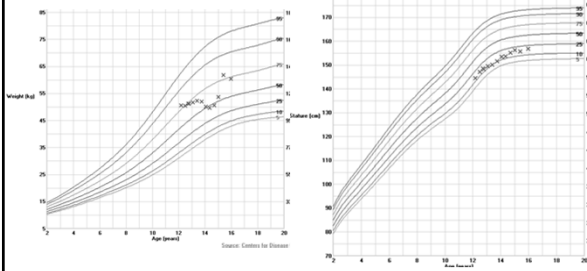
- Laboratory Analysis
 - Random cortisol of 23 ug/dL
 - Aldosterone 3.6 ng/dL (supine 2-22; upright 4-48)
 - Plasma renin activity 12814 ng/dL/hr (50-300)
- Positive 21-OH antibody
- Hyponatremia resolved (1/7/08 Na = 135)
- Continued muscle pain, fatigue
- ACTH stim testing 2/08



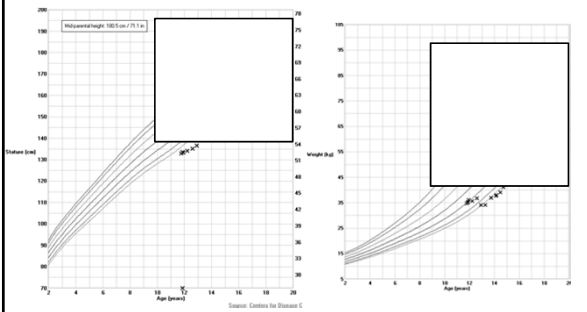
Take home message

- Consider AD in patients with other autoimmune endocrine disorders
- Marked by presence of 21-hydroxylase antibodies
- Clinically:
 - Hyponatremia not responsive to fluid resuscitation
 - In a known diabetic, increased hypoglycemia, decreasing insulin dose, weight loss, decreasing A1c
 - Non-specific complaints of abdominal pain, muscle pain, increased pigmentation
 - Can have a very insidious onset

Patient with Turner syndrome and Hypothyroidism



11 year old male with celiac disease



16 year old male with Down syndrome, T1D

- Developed progressive muscle weakness with refusal to walk
- Laboratory evaluation revealed:
 - Calcium = 4.3 mg/dL (normal 8.9-10.7)
 - Phos = 2.8 mg/dL (normal 3-5.2)
 - Alk Phos = 1063 U/L (normal 58-237)
- Laboratory evaluation suggestive of vitamin D deficiency – But why?
- Further laboratory evaluation confirmed multiple vitamin deficiencies including vitamin D
- TTg was markedly elevated = 4879 (greater than 30 is strongly positive!)
- Treatment with gluten free diet and dietary supplementation of vitamin D and calcium resulted in improved calcium and Vitamin D and ability to walk

SUMMARY

Historical clues

- Screen patients with T1D, Down syndrome and Turner syndrome for symptoms:
 - Thyroid disease
 - Symptoms can be non-specific
 - Celiac disease
 - Children may be asymptomatic
 - Addison's disease
 - Unique symptoms in T1D: increased hypoglycemia, decreased insulin requirement and A1c
- Growth chart can provide valuable information
 - Decreased height (hypothyroidism)
 - Weight loss (celiac disease, Addison's disease, hyperthyroidism)

Physical examination findings

- Vitals
 - Increased heart rate and blood pressure – hyperthyroidism
 - Orthostatic hypotension – Addison disease
- Thyroid enlargement
- Skin
 - Pigment – Addison disease
 - Dermatitis Herpetiformis – Celiac disease

Disorder	Thyroid	Celiac
Type 1 diabetes	Screen annually	Screen at onset and with symptoms Some recommend screening every several years
Down syndrome	Screen with NBS, 6 months 12 months of age and then annually	Screen once eating gluten and after age 3 years Screen every several years
Turner syndrome	Screen annually: starting at age 4 years	Screen once eating gluten and after age 3 years Screen every several years

No recommendations for screening for thyroid in patients with celiac
 No recommendations for screening for celiac in patients with thyroid
 No recommendations for screening for Addison's disease in patients with T1D

Jennifer.barker@childrenscolorado.org

QUESTIONS?
