A WOLF IN SHEEP'S CLOTHING: Curve Balls in Common Endocrine Disorders.

Dr Adi E Mehta, MD, FRCPC,FACE.

Staff, Endocrine & Metabolic Institute,

Cleveland Clinic

CASE

- 23 yr old student
  - Weight gain 10 lbs in 6 mths
  - Nocturia recent onset
  - No significant past history
  - Family History : DM in grandfather and father
- Examination
  - Weight 175 lbs Height 69 in BMI 27 kg/m2
  - **BP 122/84 P 76/min**
- **Biochemistry**
  - **FBS 136 mg/dL HbA 7.5%**
  - **Cholesterol 162 TG 140 HDL 43 LDL 84 mg/dL**
  - **S. Creatinine 0.9 mg/dL U Microalbumin 70 ugm**
  - **GAD-65 Negative**

DIFFERENTIAL Dx

- Dx Diabetes:
  - ? Type 1 – young, lean
  - ? Type 2 - Non ketotic, weight
  - ? MODY

DIFFERENTIAL Dx

- Dx Diabetes: ? Type 1 – young, lean
  - ? Type 2 - Non ketotic, weight gain
  - ? MODY
- Why MODY? – Features of MODY
  - Young - Age < 25 yrs
  - Minimally overweight – frequent MODY feature
  - Gaining weight , no ketosis – therefore has insulin
  - 3 generations affected - Autosomal dominant
  - Absence of autoantibodies
- THUS NEEDS GENETIC TESTING

Monogenic Forms of Diabetes

- Forms associated with INSULIN RESISTANCE
- Forms associated with DEFECTIVE INSULIN SECRETION
  - Maturity Onset Diabetes of the Young (MODY)

Phenotypic Expression and Natural History of MODY

- Recognition at young age
  - Under age 25 years
  - 7-13 years or younger, if sought by glucose testing in younger generations
- Not progressive, or slowly progressive
  - Hyperglycemia responsive to diet and/or oral anti-hyperglycemic agents for years to decades
  - May progress to insulin-requiring diabetes (not insulin-dependent or ketosis-prone)
  - May progress rapidly from young age onward

Maturity Onset Diabetes of the Young (MODY)

- 1975 Definition:
- Type 2 Diabetes in young patients (<25-30)
- PLUS
- Autosomal dominant inheritance

Current Definition of MODY

- Heterozygous ***Monogenic*** mutations in one of the 6 different genes implicated to date
- Autosomal dominant inheritance
- Onset of Diabetes early in life:
  - Childhood, adolescence or young adulthood (<25 yrs)
- Primary defect in insulin secretion

Heterozygous Gene Mutations Identified in MODY

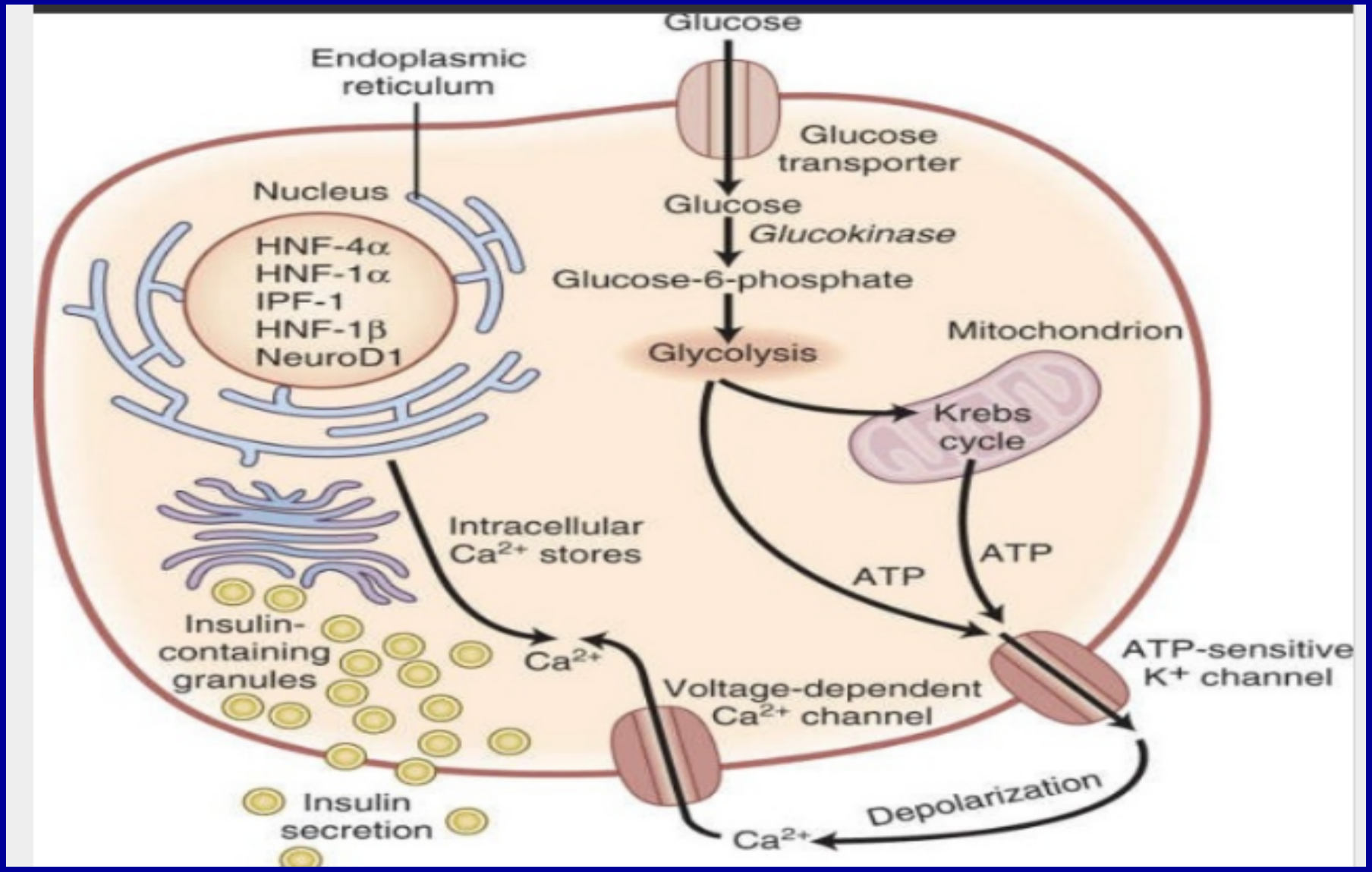
Name	(Year)	Gene	Chromosome
MODY1	(1991)	HNF-4α	20q
MODY2	(1993)	Glucokinase	7p
MODY3	(1996)	HNF-1α	12q
MODY4	(1997)	IPF-1 (PDX-1)	13q
MODY5	(1997)	HNF-1β	17q
MODY6	(1999)	Neuro-D1 / BETA-2	2q

HNF = Hepatocyte nuclear factor

IPF = Insulin promoter factor

PDX-1 = Pancreatic duodenal homeobox-1

INTRACELLULAR SITES OF DEFECTS CAUSING MODY



Liver-Enriched Transcription Factors: HNF-1 alpha, HNF-1 Beta & HNF-4 alpha

- Expressed in the liver, pancreatic islets, kidneys and genitalia
- In Beta cells, they regulate
  - The expression of the insulin gene
  - Proteins involved in glucose transport and metabolism
- Mutations result in defects of insulin secretion in response to glucose, leading to progressive hyperglycemia
- MODY 1 & 3 respond to sulfonylureas initially

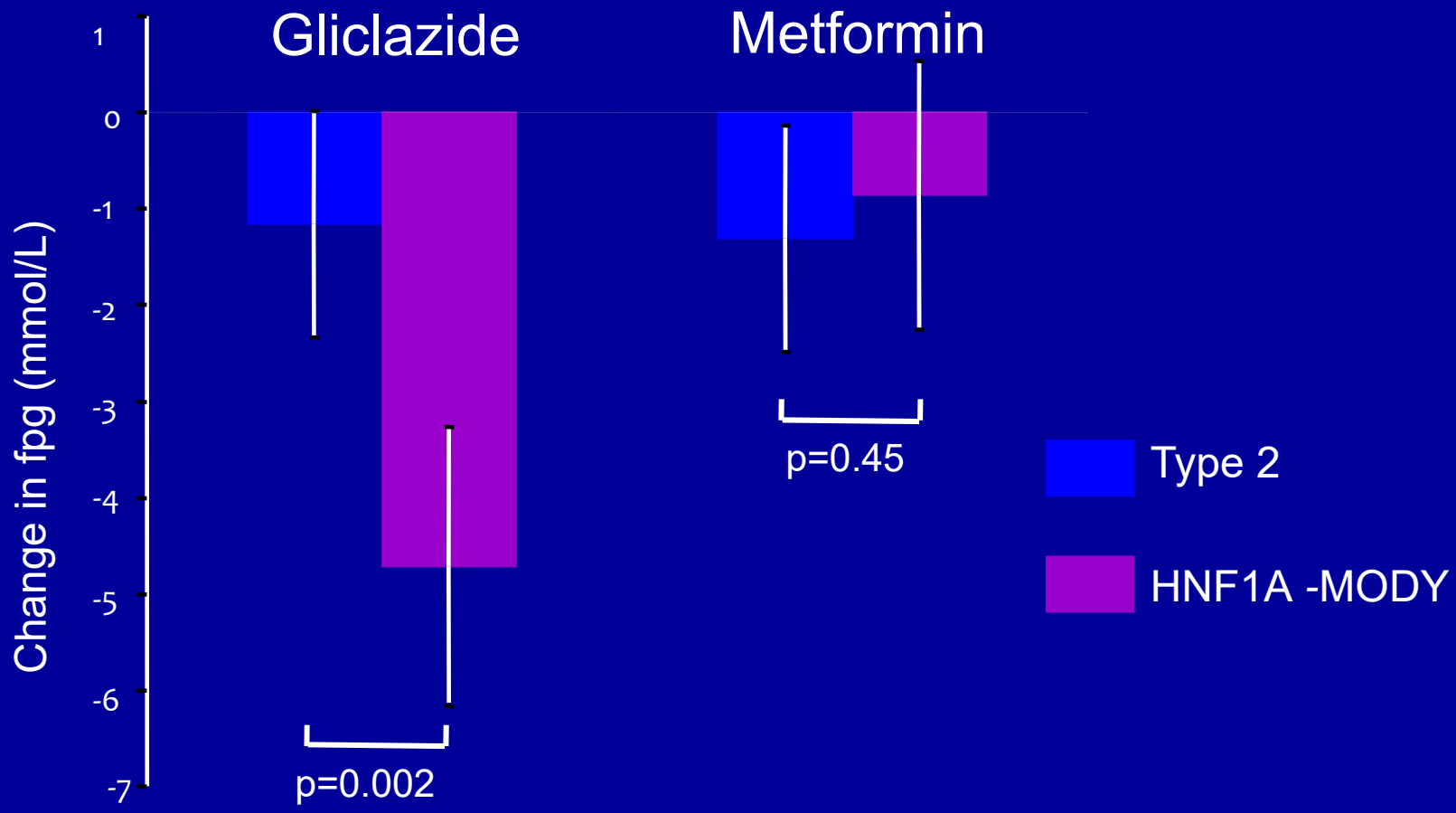
MODY1 (HNF-4α Mutation): Possible Early Defects in Insulin Secretion

- **Methods:**
  - Bergman's minimal model: Frequently sampled IV GTT
  - Polonsky's low-dose glucose infusion to measure insulin secretion rate (ISR) & pulse analysis
- **Conclusions:**
  - Non-diabetic members: Deranged and deficient insulin secretion; no insulin resistance. Apparently the primary inherited abnormality causing susceptibility to diabetes.
  - Diabetic members: Deranged and deficient insulin secretion; any decrease in insulin action is secondary to hyperglycemia

HNF1A/HNF4A-MODY 1&3

- Normoglycaemic in childhood
- Progressive β-cell dysfunction
- Diabetes presents in 2nd-4th decade
- Maintain some endogenous insulin production (diabetic ketoacidosis rare)
- Complication profile similar to type 1 diabetes
- Sensitivity to sulphonylureas (SU)

SU sensitivity in HNF1A-MODY



Pearson *et al* (2003) Lancet

MODY-Related Proteins [1/4]

- Glucokinase
  - Expressed in β-cells and liver
  - Catalyzes transfer of phosphate from ATP to glucose, generating glucose-6-phosphate, a rate-limiting step in glucose metabolism
  - "Glucose sensor" in β-cells
  - Facilitates glycogen synthesis in the liver
  - Mild stable hyperglycemia
  - Does not respond to sulfonylureas

Glucokinase (*GCK*) MODY

- Mild lifelong fasting hyperglycaemia
- FPG 5.5-8.5 mmol/l, HbA1c <8%
- Rise in blood sugar after glucose load similar to non-diabetic (<3.5 mmol/l)
- Asymptomatic – diagnosed during routine screening
- Low level of diabetic complications (no sight threatening retinopathy in 50 yrs of GCK-MODY)

Treatment of GCK -MODY

- No trial data
- Observational data suggests treatment does not change HbA1c
- Recommend annual HbA1c in primary care
- Can get Type 2 diabetes if insulin resistant

Distinguishing Clinical Characteristics of MODY and Type 2 Diabetes (DM2) [1/2]

- Mode of inheritance
  - MODY: Monogenic, autosomal dominant
  - DM2: Polygenic
- Age of onset
  - MODY: Childhood, adolescence, usually <25 years
  - DM2: Usually 40-60 years; occasionally in obese adolescents
- Pedigree
  - MODY: Multi-generational
  - DM2: Rarely multi-generational

Distinguishing Clinical Characteristics of MODY and Type 2 Diabetes [2/2]

- Penetrance
  - MODY: 80-95 %
  - DM2: Variable (10-40 %)
- Body habitus
  - MODY: Not obese
  - DM2: Usually obese
- Dysmetabolic syndrome
  - MODY: Absent
  - DM2: Usually present

When To Suspect MODY

- Patient with “Type 1” diabetes - Negative antibodies
- Patient with “Type 1” diabetes – very positive C peptide, or proinsulin for years post diagnosis
- Patient with “Type 2” diabetes – normal weight and no evidence for insulin resistance (eg. N HDL)
- Patient with diabetes and a 2-3 generation history of diabetes developing while young
- Patient with diabetes and idiopathic pancreatic insufficency especially if young (<25 yrs of age)
- Individual or family history of diabetes and developmental renal disease or renal cysts

Table 2

Features that may help differentiate Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus and MODY.

	Type 1 DM	Type 2 DM	MODY
Frequency	Common	Increasing	2 – 5% of non - insulin dependent Diabetics
Genetics	Polygenic	Polygenic	Autosomal Dominant
Family History	<15%	>50%	100%
Ethnicity	Different races	Asians, Polynesians, Indigenous Australians	Different races
Age of onset	Throughout Childhood	Post-Puberty	<25 yrs
Severity of onset	Acute and severe	Mild	Mild/Asymptomatic
Ketosis / DKA	Common	Uncommon	Rare

Genetic Testing

- Only definitive way of establishing/confirming the diagnosis
- Source – blood or saliva
- Not all mutations cause disease
- Each child has a 50% chance of inheriting the disease
- 1st degree relatives have a 50% chance of carrying the same gene mutation and a >95% chance of developing diabetes at some time in their life

Treatment of MODY

- Treatment depends on the involved gene and other factors
- MODY 1&3 respond to high dose sulfonylures by stimulating insulin secretion
- MODY 2 does not require any therapy
- Other types of MODY may require multiple daily injections of insulin.

MODY: Take Home Message

- Suspect MODY in young relatively lean patients with hyperglycemia
- Autosomal dominant so 3 consecutive generations affected
- No Ketosis
- No Beta cell autoimmunity
- Normal C peptide

Case

- 33 yr old female,with a 4 yr history of Hypothyroidism
- On treatment with L thyroxine
- After an initial improvement in symptoms, continues to have symptoms: fatigue, dry skin and hair, brittle nails, puffiness and bloating, constipation, irregular menses, wt gain and difficulty losing wt
- Exam: BP 126/78 P 64 Wt 156 lbs ht 65 in BMI 27.7 kg/m2, palpable 35 gm firm diffuse mobile non tender goiter

Laboratory Results

- CBC: Hgb 10.9 g/dl MCV & MCHC low
- CMP: Mild transaminitis
- Vitamin D 16 to 23 on 5000 units daily
- TFTs:

	TSH	Free T4
At Dx	14	0.7
On T4 50 ugm	5	0.8
On T4 100 ugm	4	0.9
On T4 125 ugm	3.8	0.9
On T4 150 ugm	3.6	0.95
On T4 200 ugm	3.3	1.0 (latest)

Case Synopsis

- Exaggerated Hypothyroid symptoms with marginally normal thyroid indices
- Limited response to L thyroxine dose escalations
- Anemia – iron deficiency
- Vitamin D insufficiency

Celiac Disease: Clinical Manifestations in Adults

In a study of 1138 people with biopsy–proven celiac disease:

- Majority of individuals were diagnosed in their 4th to 6th decades.
- Women predominated (2.9:1)- the female predominance was less marked in the elderly.
- Diarrhea was the main presenting symptom occurring in 85%.
- 36% had a previous diagnosis of irritable bowel syndrome.
- Symptoms were present a mean of 11 years before diagnosis.

Green PHR, et al. Characteristics of adult celiac disease in the USA: results of a national survey. Am J Gastroenterol 2001;96:126–131.

Celiac Disease: Clinical Manifestations in Adults

In a population-based study from Minnesota, Murray et al noted a 10-fold increase in the incidence of celiac disease from 1950 to 2001.

- The clinical severity of the disease decreased, with fewer people with diarrhea and weight loss at presentation.
- Only 54% had diarrhea at diagnosis, 34% abdominal pain and 30% bloating.
- Obesity was present in 27%.

Murray JA, et al. Trends in the incidence and clinical features of celiac disease in a North American community, 1950-2001. Clin Gastroenterol Hepatol 2003;1:19–27.

Changing Spectrum of Celiac Disease

Few if any GI symptoms

Marked GI symptoms

Fatigue
Depression, irritability
Menstrual irregularity
Weakness
Infertility
Growth Disturbance
Neurologic Complaints

Diarrhea
Bulky, Pale, Foul stools
Abdominal Distension, Bloating
Abdominal cramps
Weight loss
Loss of or increased appetite

KAGNOFF, MF. “Overview and Pathogenesis of Celiac Disease” GASTROENTEROLOGY 2005;128:S10–S18

Clinical Presentation

- Mild, chronic diarrhea or Occasional constipation
- Lactose intolerance
- Dental enamel hypoplasia
- Osteopenia / osteoporosis
- Unexplained microcytic (Fe) / macrocytic (folic acid) anemia
- **Can be asymptomatic!**

Laboratory Features

- Gliadin IgA/IgG
- Reticulin IgA
- Endomysial IgA
- Tissue Transglutaminase IgA
- **3-5% of celiac patients are IgA deficient!**
- IgA deficiency: False-negatives
- None of the tests have 100% sensitivity and specificity (false-negatives / false-positives).

Increased rate of *Giardia*

Laboratory Features

Antigliadin antibody

- Antigliadin IgG: sens. 90-100%, spec. 60%.
- Antigliadin IgA: sens. 60-100%, spec. 86-100%
- Ab titers and sensitivity of IgG and IgA tend to decrease as patient's age increases (>3yrs old).

Laboratory Features

Antiendomysium antibody (IgA)

- Sensitivity: close to 100%
- Specificity: close to 100%
- Antibody to unknown antigen

Laboratory Features

Tissue transglutaminase antibody (TTG)

- Probably the sole autoantigen recognized by the antiendomysium Ab.
- High affinity for gliadin proteins
- Almost 100% sensitivity and specificity
- Now the antibody test of choice.

Diagnostic Testing

- Once antibody tests positive, duodenal biopsy is key to diagnosis (absolute 100% sensitivity and specificity).
- Hyperplastic crypts
- Increased mitotic figures
- Villi flattened / gone
- Dense lymphocytic infiltrate with plasma cells
- Disaccharidases: Brush border hydrolases are decreased, especially lactase (lactose intolerance).

Diagnostic Test

- There is a spectrum of insult…

Absent villi  Villi present

- There is always a lymphocytic infiltrate that goes away with dietary manipulation.

Treatment

Removal of gluten from the diet is essential!

Treatment

- Histological celiac disease at time of diagnosis.
- Clinical recovery is evident after gluten removal.
- Ab levels return to normal after diet restriction.
- Systemic disturbances resolve quickly.
- Abdominal symptoms resolve over a few weeks.
- Villi resume normal architecture in one year.
- “Safe” gluten intake < 50mg/day

Associated Diseases

- Higher incidence of autoimmune diseases overall than the normal population.
- May be due to the shared HLA haplotypes between diseases.
- Seems to be related to duration of gluten exposure.

Gut-thyroid axis and celiac disease

Table 1

Shared clinical features between celiac and autoimmune thyroid diseases.

Symptom/sign	Celiac disease	Hashimoto's thyroiditis	Graves' disease
Weight	Loss	Gain	Loss
Bowel movement	Diarrhea/constipation	Constipation	Diarrhea
Joint/bone pain	+/+	+/−, hypotonia	Muscle weakness
Fatigue/tiredness	+	+	+
Psychology	Depression, anxiety	Depression	Anxiety, nervousness, restlessness, attention and concentrating difficulties
Hair loss	+	+	+/− Alopecia
Infertility/missed periods	+/+	+/+	+/+
Miscarriage	+	+	+
Increased other autoimmune diseases	+	+	+

Comparison of Features Between Celiac Disease and Hashimoto's Thyroiditis

	Celiac disease	Hashimoto thyroiditis
Incidence	1–1.5%, increases	5%, increases
Gender predominance	Female	Female
Geoepidemiology	Increasing incidence	Increasing incidence
Environmental factors	Gluten, microbial mTg, infection, stress, formula feeding, increased diversity of dysbiota	Infection, diet, iodine, medications, smoking
Associated infections	Enterovirus, EBV, CMV, HBV, HCV, rotavirus *Bacteroides* species, *Campylobacter jejuni*, *pneumococcus*, tuberculosis and *Helicobacter pylori*	EBV, Yersinia enterocolitica, Helicobacter pylori, HCV, CMV, Borrelia burgdorferi
Dysbiota	Decreased diversity	?
HLA predisposition	DQ-2, DQ-8	HLA-DRβ1-Arg74, DQ-2
Autoantibodies	tTg, DGP, EMA, neo-epitope tTg, neo-epitope mTg	Anti-thyroid peroxidase, anti-thyroglobulin
Autoantigen	tTg	Thyroid peroxidase, thyroglobulin
Potential inducer enzyme (PTMP)	tTg, mTg deamidation/cross-linking	TTg
Adaptive/innate immunity	+++	+++
Target/associated organs	Small bowel/joint, bone, endocrine, heart, lung, liver, kidney, skin, nerves, etc.	Thyroid
Therapy	Gluten free diet	Symptomatic, thyroid replacement therapy

CMV, cytomegalo virus; DGP, diamidated gliadin peptide; EBV, Epshtein Bar virus; EMA, endomysial antibodies; HBV, hepatitis B virus; HCV, hepatitis C virus; mTg, microbial transglutaminase; tTg, tissue transglutaminase.

Gut-thyroid axis and celiac disease

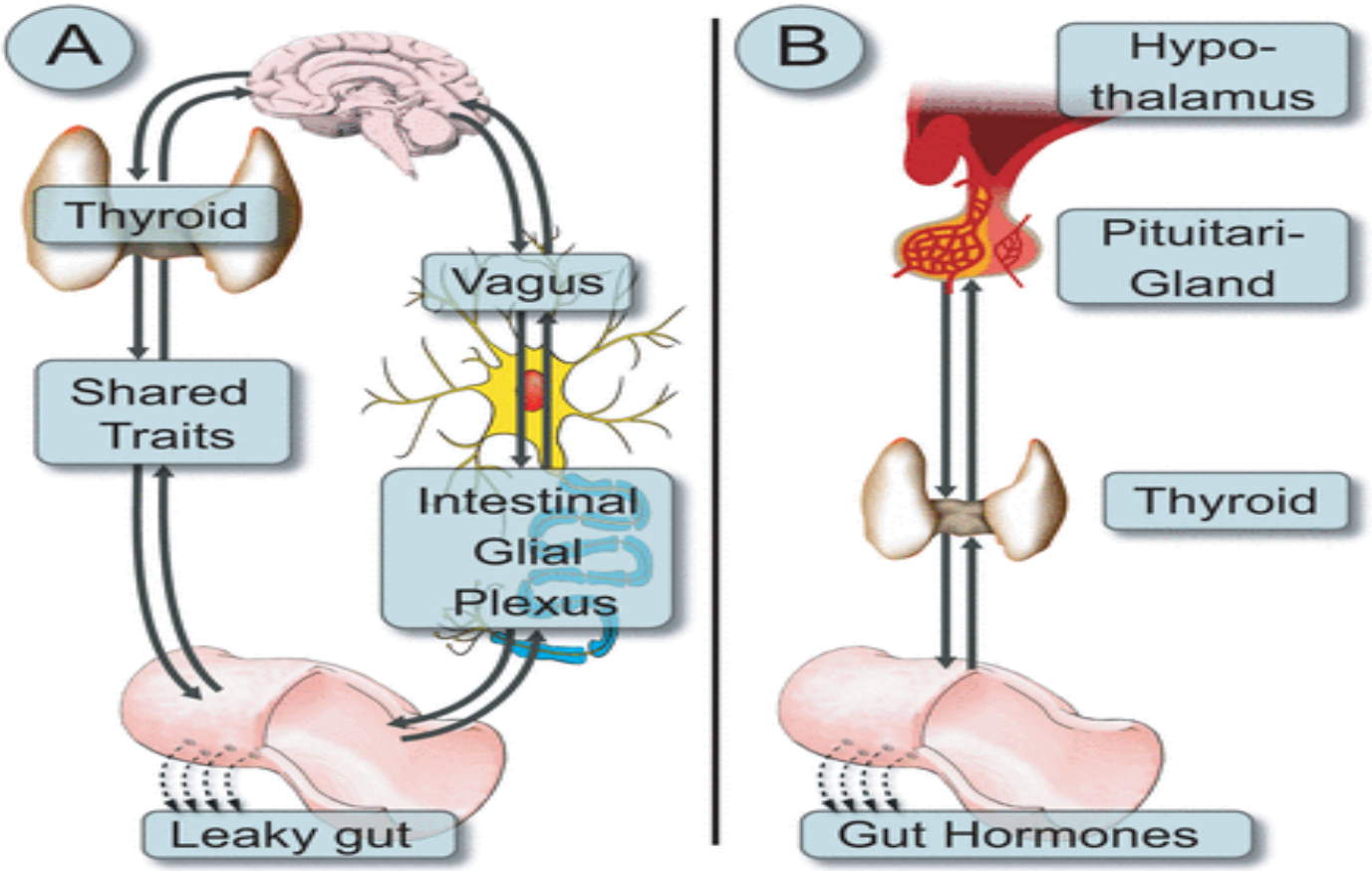


Figure 1

A schematic presentation of (A) the bidirectional neuronal pathways connecting the thyroid through the vagal nerve to the intestinal neuronal plexus, finally inducing leaky gut. Parallel, multiple gut-thyroid shared traits (epidemiology, autoantibodies, genes, immune pathways and autoimmune diseases) influence the gut-thyroid axis; (B) the hormonal bidirectional cross-talks between the hypothalamus-pituitary-thyroid-gut hormones axes.

Celiac Disease: Autoimmune Thyroid Disease

- One study of 83 patients with autoimmune thyroid disease found a frequency of celiac disease of 4.8 percent
- An epidemiologic study of 335 patients diagnosed with celiac disease between 1980 and 1990 determined that 5.4 percent of the patients with celiac disease also had autoimmune thyroid disease

Collin P, Reunala T, Pukkala E, Laippala P, Keyrilainen O, Pasternack A. Coeliac disease--associated disorders and survival. Gut 1994;35:1215-8.
Collin P, Salmi J, Hallstrom O, Reunala T, Pasternack A. Autoimmune thyroid disorders and coeliac disease. Eur J Endocrinol 1994;130:137-40

Celiac Disease: Other Autoimmune Endocrine Disorders

AI diseases	*CD patients (n (%))*	*Controls (n (%))*	*χ^2 test (p value)*
IDDM	16 (3.79)	2 (0.33)	15.341 (<0.0005)
Dermatits herpetiformis	42 (9.95)	0 (0)	60.269 (<0.0001)
AI thyroid diseases	57 (13.5)	12 (2)	50.852 (<0.0001)
AI hepatitis	2 (0.5)	1 (0.16)	0.952 (NS)
AI atrophic gastritis	3 (0.71)	0 (0)	2.218 (NS)
AI anaemia, neutropenia, thrombocytopenia	7 (1.65)	1 (0.16)	5.371 (=0.0218)
Connective tissue diseases	7 (1.65)	15 (3.19)	0.455 (NS)
Psoriasis	13 (3.08)	36 (5.95)	3.897 (=0.0488)
Alopecia	1 (0.24)	3 (0.5)	0.021 (NS)
Epilepsy with occipital calcifications	3 (0.7)	0 (0)	2.218 (NS)

In study of 605 controls and 422 patients (aged 16–84 years): 30% of adult patients with CD had at least one AI disease with an overall 2–3-fold higher frequency than controls.

Guidetti, CS, et al. Duration of gluten exposure in adult coeliac disease does not correlate with the risk for autoimmune disorders,Gut 2001;49:502–505

Celiac Disease: Iron Deficiency Anemia

- In a study of 227 patients with biopsy–proven celiac disease- iron-deficiency anemia was the mode of presentation in 8%[1]
- In a Mayo Clinic study, celiac disease was identified as the cause of iron deficiency in 15% of those undergoing endoscopic assessment for iron deficiency.[2]
- In a prospective study of adults, mean age in their 50s, Karnum et al found 2.8% to have celiac disease.[3]

1. Lo W, Sano K, Lebwohl B, Diamond B, Green PH. Changing presentation of adult celiac disease. Dig Dis Sci 2003;48:395–398.
2. Oxentenko AS, et al. The insensitivity of endoscopic markers in celiac disease. Am J Gastroenterol 2002;97:933–938.
3. Karnam US, et al. Prevalence of occult celiac disease in patients with iron-deficiency anemia: a prospective study. South Med J 2004;97:30–34.

Celiac Disease: Vitamin D Deficiency

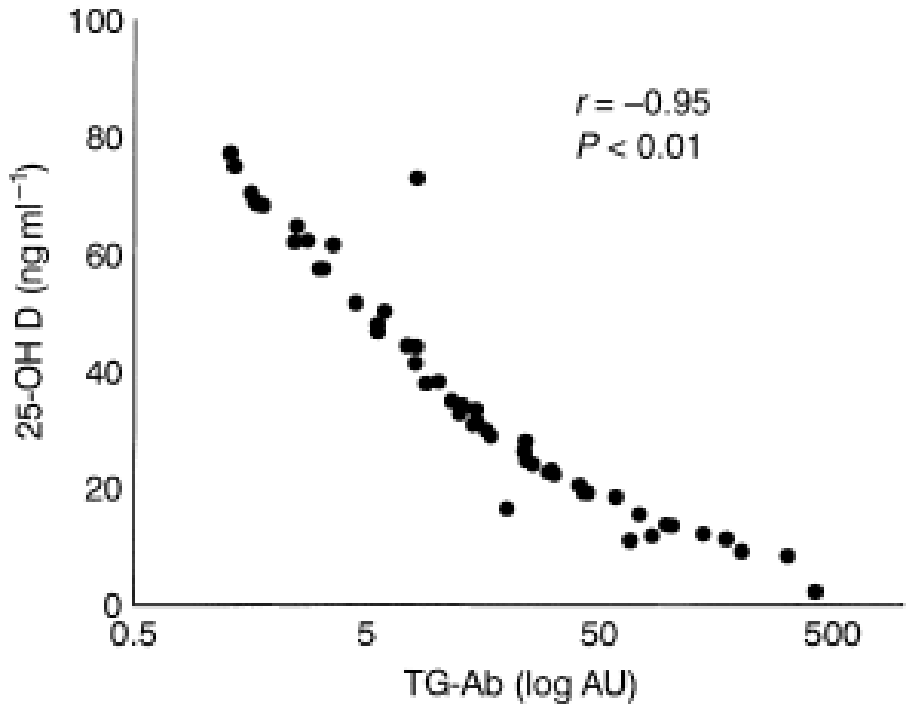


Fig. 2 Relationship between serum antibodies to tissue transglutaminase (log normal) and serum 25[OH]D levels.

- 255 women with osteoporosis
- 53 women tested positive for tTG ab
- Prevalence of serological disease 9.4%

Nuti, R et al. Prevalence of undiagnosed coeliac syndrome in osteoporotic women. Journal of Internal Medicine 2001; 250: 361±366

Celiac Disease: Vitamin D Deficiency

	TG-ab+ ($n = 24$)	Control group ($n = 231$)	P
Age (years)	65.7 ± 9.2	66.7 ± 8.4	NS
Weight (kg)	61.2 ± 10.2	60.6 ± 9.4	NS
Height (cm)	161 ± 11.3	158.7 ± 6.6	NS
Lean mass (kg)	36.7 ± 4.0	36.6 ± 4.0	NS
Fat mass (kg)	21.6 ± 5.9	22.5 ± 6.6	NS
U-calcium/creatinine (mg g^{-1} 24 h)	252 ± 110	263 ± 115	NS
U-Phosphorus (mg 24 h^{-1})	873 ± 331	954 ± 336	NS
U-crosslaps (µg $mmol^{-1}$ creatinine)	288 ± 88	270 ± 90	NS
S-PTH (pg mL^{-1})	65.1 ± 29.7	35.1 ± 20.0	< 0.001
S-25- (OH)D (ng mL^{-1})	17.8 ± 7.2	55.1 ± 20.3	< 0.001
S-TG-ab (AU)	88.3 ± 101	6.8 ± 4.3	< 0.001

NS = not significant.

Nuti, R et al. Prevalence of undiagnosed coeliac syndrome in osteoporotic women. Journal of Internal Medicine 2001; 250: 361±366

Bottom Line…

- Celiac disease is more common than we realize.
- The phenotypic presentation is changing, may be mild and non specific.
- Ab tests have excellent sensitivity and specificity (esp. EMA and tTG).
- Gluten free diet is mandatory and curative.
- Keep in mind high risk & coexistence of celiac disease with other autoimmune disorders.
- Screen 1st degree relatives.

CASE

- 34 y/o female presented with sudden and progressive onset of episodes of lightheadedness and palpitations, debilitating Fatigue and “foggy” concentration
- The first episode noted after a significant flu like illness and first occurred during groceries shopping : noted all colors brighter, out of body spacy feeling ?, dizzy , fluttering , pounding palpitations & Foggy thinking and concentration
- She stopped driving due to a feeling of cars coming towards her

CASE

- PAST MEDICAL HISTORY

- None
- Unlisted Laparoscopy Procedure, Ute - 11/2007 (ovarian ectopic)

- FAMILY HISTORY

- Mother: Thyroid (hyper), other (Sarcoidosis)
- Father: other (Headaches)
- Maternal Grandmother: Hypertension (age 70s/great and stroke), Breast Cancer (twice, age 49, age 75)
- Paternal Grandmother: Osteoporosis, Cervical Cancer
- Maternal Aunt: Thyroid (4/7 aunts w/ one w/ hypo, others hyper), Breast Cancer (great age 38)

CASE

- BP 99/67 | Pulse 80 | Ht 165.5 cm (5‘ 6) | Wt 55. kg (121 lb) | BMI 21.2 kg/m2 |
- GENERAL: Well nourished, well hydrated, in no distress and oriented x 3
- EYES: no thyroid eye signs and lid lag no
- NECK: no visible nodules or goiter, no bruit, no tenderness and no nodes
- THYROID: smooth, non-tender, 25 gram, firm and No palpable nodules
- EXTREMITIES: No clubbing, no edema, no cyanosis and normal nails
- NEURO: normal strength and no tremor

CASE - synopsis

- Fatigue
- Out of body experience
- Episodic Palpitations
- Postural hypotension
- Irregular heavy periods
- **DIFFERENTIAL**
- R/O thyroid dysfunction including antibodies
- R/O Pheochromocytoma
- R/O Reactive Hypoglycemia
- R/O Cardiac etiology ? MVP ?Aberrant cardiac rhythmes
- If ALL negative consider POTS, celiac disease, anemia or sarcoidosis

Types of Orthostatic Hypotension

- Initial Orthostatic Hypotension
- Orthostatic Hypotension
  - Non-neurogenic orthostatic hypotension
  - Neurogenic orthostatic hypotension
- POTS
  - Neuropathic POTS
  - Hyperadrenergic POTS
- Vasovagal Syncope

Postural Orthostatic Tachycardia Syndrome

- Definition: chronic day-to-day symptoms of **orthostatic intolerance** plus **excessive increase in heart rate** when upright
  - HR>30 from baseline or >120 after 10 mins during tilt test in adults
  - HR>40 from baseline in children & teens
  - BP not usually low
- Cause: alterations in autonomic nervous system

Epidemiology of POTS

- Females > Males: 3:1 to 5:1
- Triggers:Onset – after flu like illness, or self limited autoimmune disease, or surgery or injury, pregnancy, growth spurt
- May be associated with joint hypermobility syndromes
- Underweight: need to differentiate from eating disorders
- Heat worsens symptoms
- Cognitive function may be affected

POTS

- Clinical Presentation:
  - Palpitations
  - Fatigue
  - Lightheadedness
  - Visual Blurring
  - Near syncope/Syncope - rare
  - Tremulousness
  - Anxiety
  - Nausea, abdominal cramps, early satiety, bloating, constipation, and diarrhea
  - Headaches
  - Exercise intolerance

POTS - Investigation

- Tilt Table Test:
  - A significant drop in blood pressure
  - An exaggerated increase in heart rate when tilt table vertical.

POTS - Etiology

May result from an underlying autonomic neuropathy that may be:

post viral.- Many cases originate after systemic infection usually viral

or immune-mediated in origin:

- ganglionic acetylcholine receptor antibodies in some patients
- Beta adrenergic receptor gain of function autoantibodies
- Alpha Adrenergic receptor loss of function autoantibodies

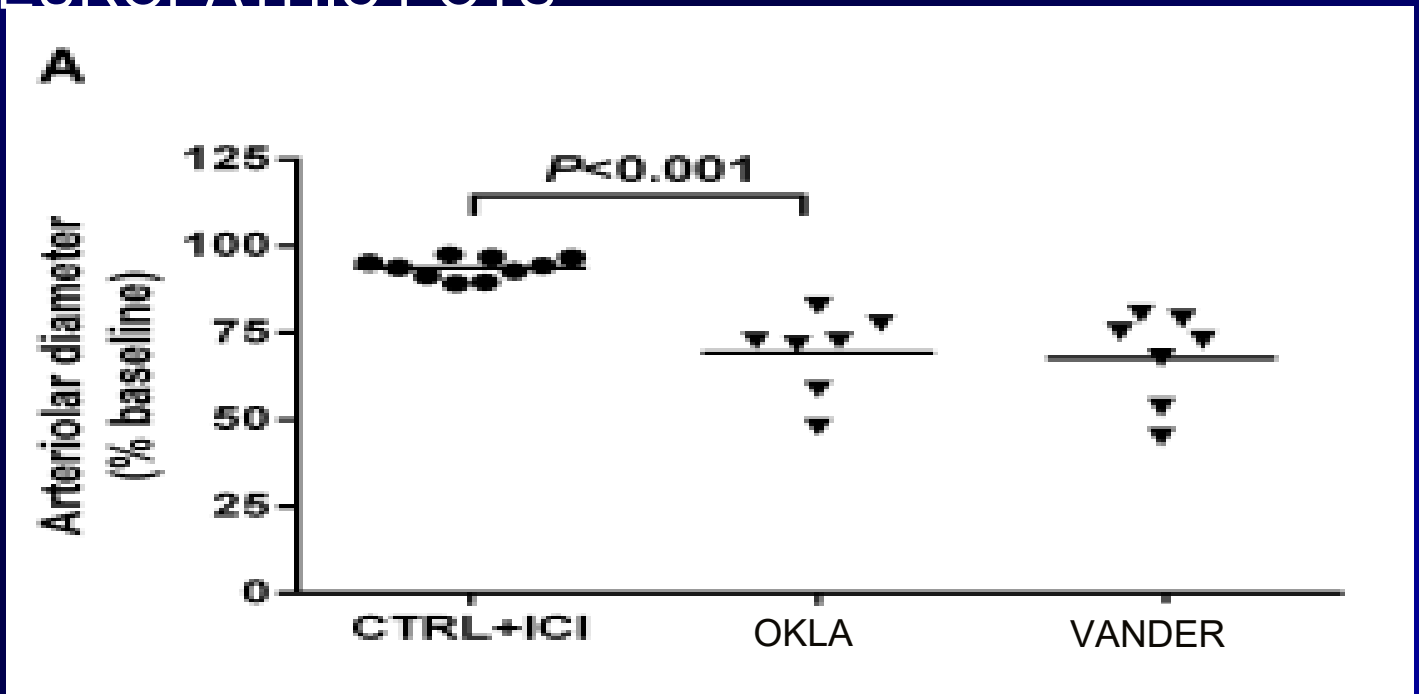
- Patients with POTS frequently experience symptomatic improvement with saline infusion.

Types of POTS

- Neuropathic POTS
  - Cause:-loss of regional vasoconstrictive ability
  - Blood poling in lower extremities
  - Heart rate increases to compensate for decreased circulating blood volume due to lower limb pooling

New Developments – Autoantibodies in POTS

- Alpha Adrenergic receptor loss of function autoantibodies are present in POTS patients
- This would cause loss of normal vasoconstriction in POTS patients
- ?NEUROPATHIC POTS



Treatment of Neuropathic POTS

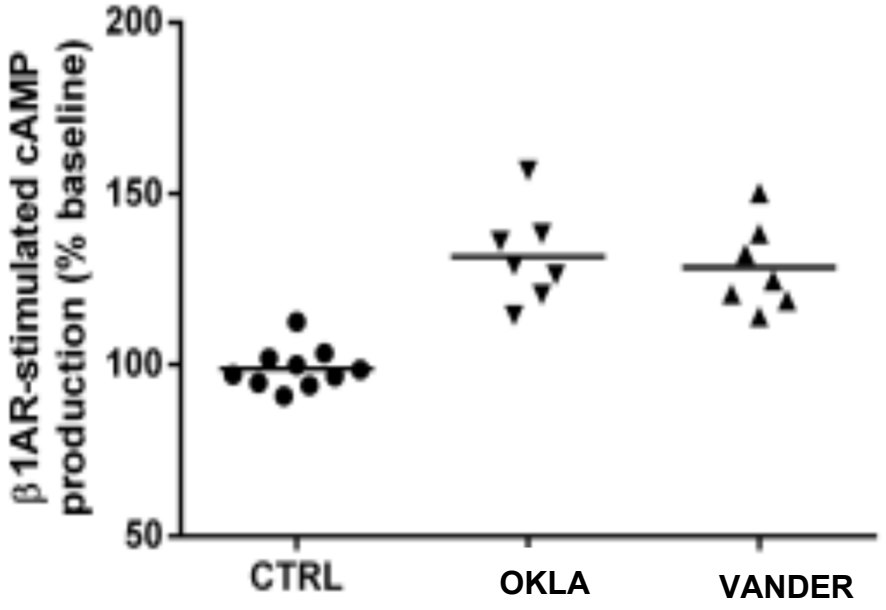
- Try to compensate for loss of regional vasoconstictive ability
  - Physical counter maneuvers – compression therapy
  - Salt and water loading
  - Midodrine
  - Mestinon
  - Exercise
  - Rapid water ingestion

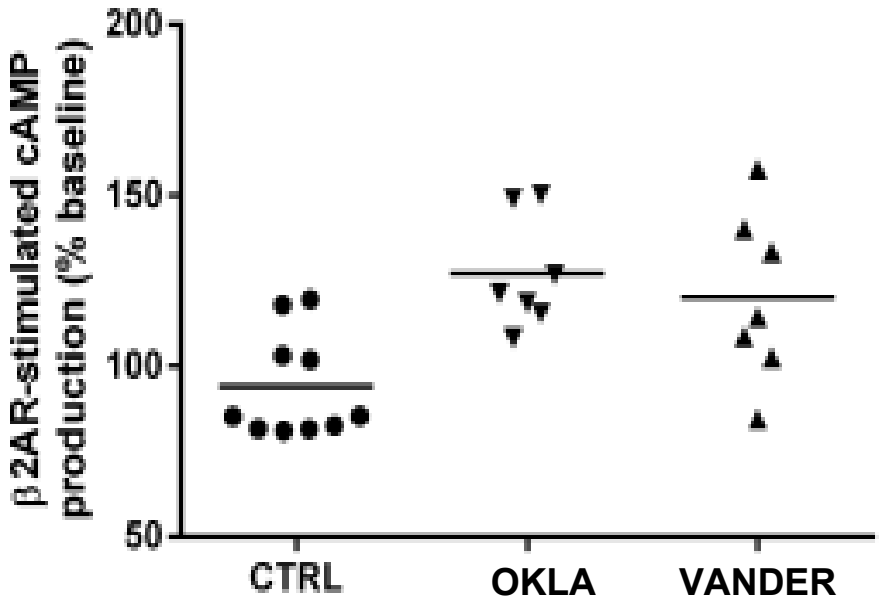
Types of POTS

- Hyperadrenergic POTS
  - Increased circulating norepinephrine
  - May have increased orthostatic blood pressure decreases
  - Less common than neuropathic form
  - Attributed symptoms – anxiety, tremor, cold sweaty extremities

New Developments- Autoantibodies in POTS

- Beta adrenergic receptor gain of function autoantibodies are present in POTS patients
- Increase in beta 1 activity would cause the increased heart rate in these patients, increase in beta 2 activity would decrease blood pressure
- HYPERADRENERGIC POTS





Treatment of Hyperadrenergic POTS

- Defect: Adrenergic potentiation
  - Physical counter maneuvers
  - Beta blockers
  - Angiotensin receptor blockers
  - fludrocortisone

POTS – long term

- Adolescent-onset: 80% recover by mid 20s
- Adult-onset: most recover within 2-5 years
- Some patients suffer long term disability associated with POTS

POTS - Summary

- POTS is a form of chronic orthostatic intolerance:
  - ?autoimmune
  - Circulatory system not responding appropriately to autonomic inputs
  - Hyperadrenergic state
  - Chronic bed rest and deconditioning