# 62F with Worsening T2DM and Newly diagnosed Autoimmune Ataxia

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# HPI

- 62F with Hx of well controlled DM admitted for fall to Neurology service
- Hx of gait difficulty since June 2016
- Evaluated in Neurology clinic prior to presentation and there was concern for cerebellar dysfunction given wide based gait
- Extensive workup unremarkable except significantly elevated GAD Abs
- Diagnosed with GAD Ab related autoimmune ataxia
- Consulted for worsening BG control on insulin regimen

## PMH

- T2DM, A1c 6-7%
- HTN

## PSH

- Hysterectomy

## FH

- Mother: DM, HTN, heart dz
- Father: Heart disease
- Sister: Breast cancer, SCD
- Sister: Lymphoma
- Daughter: SCD

## Meds

- Metformin 1000mg bid
- glipizide 5mg bid
- Victoza
- Levemir 10U Qd and novolog 10U TID
- Enalapril 20mg bid

Go to now | 12/20/2016 | 12/20/16 - 12/21/16

1 hr | 2 hr | 4 hr | 8 hr | 12 hr | 24 hr | All

| | RADIOLOGY-CT-CD | | | | | | | | | RADIOLO... | Radiology-PET-DCAM | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 12/20 0700 - 12/21 0659 | | | | | | | | | 12/21 0700 - 12/22 0659 | | | |
| Time: | 1221 | 1254 | 1607 | 1720 | 1741 | 2100 | 2115 | 2128 | 0507 | 0851 | 1312 | 1617 | |
| **Glucose (mg/dL)** | Graphs cannot display in the current view | | | | | | | | | | | | |
| **Accucheck** | | | | | | | | | | | | | |
| POC Glucose | 171 | | 188 | | | | 343 | | | 334 | 284 | 411 | POC Glucose |
| **Serum Glucose** | | | | | | | | | | | | | |
| Serum Glucose | | | | | | | | | 304 | | | | Serum Gluc... |
| **Insulin Dose** | | | | | | | | | | | | | |
| INSULIN ASPART SUB... | | 4 | | 2 | 4 | | | 8 | | | | | INSULIN A... |
| INSULIN GLARGINE,H... | | | | | | 10 | | | | | | | INSULIN G... |

## Diabetic Management

Go to now | 12/21/2016 | 12/21/16 - 12/22/16

1 hr | 2 hr | 4 hr | 8 hr | 12 hr | 24 hr | All

| | Radiology-PET-DCAM | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 12/21 0700 - 12/22 0659 | | | | | | | | 12/22 0700 - 12/23 0659 | | | |
| Time: | 1617 | 1630 | 1632 | 1756 | 1955 | 2224 | 2250 | 2251 | 0413 | 0821 | 0850 | 0851 |
| **Glucose (mg/dL)** | Graphs cannot display in the current view | | | | | | | | | | | |
| **Accucheck** | | | | | | | | | | | | |
| POC Glucose | 411 | | | 472 | 241 | 186 | | | | 306 | | | POC Glucose |
| **Serum Glucose** | | | | | | | | | | | | |
| Serum Glucose | | | | | | | | | 226 | | | | Serum Gluc... |
| **Insulin Dose** | | | | | | | | | | | | |
| INSULIN ASPART SUB... | | 6 | 8 | | | | 2 | | | | 8 | 6 | INSULIN A... |
| INSULIN GLARGINE,H... | | | | | | | | 16 | | | | | INSULIN G... |

Recommended increasing lantus to 20U daily and novolog 6U with meals

**Diabetic Management**

Go to now | 12/22/2016 | 12/22/16 - 12/23/16 | 1 hr | 2 hr | 4 hr | 8 hr | 12 hr | 24 hr | All

| | Radiology-PET-DCAM | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 12/22 0700 - 12/23 0659 | | | 12/23 0700 - 12/24 0659 | | | | | | | | | |
| Time: | 2112 | 2146 | 0501 | 0836 | 0847 | 0849 | 1146 | 1213 | 1216 | 1700 | 1702 | 1732 | |
| **Glucose (mg/dL)** | Graphs cannot display in the current view | | | | | | | | | | | | |
| **Accucheck** | | | | | | | | | | | | | |
| POC Glucose | 164 | | | 353 | | | 208 | | | 52 | 46 | 104 | POC Glucose |
| **Serum Glucose** | | | | | | | | | | | | | |
| Serum Glucose | | | 277 | | | | | | | | | | Serum Gluc… |
| **Insulin Dose** | | | | | | | | | | | | | |
| INSULIN ASPART SUB… | | | | | 10 | 8 | | 10 | 4 | | | | INSULIN A… |
| INSULIN GLARGINE,H… | | 20 | | | | | | | | | | | INSULIN G… |

Lantus increased to 24U and novolog 8U TID CC

**Diabetic Management**

Go to now | 12/23/2016 | 12/23/16 - 12/24/16

1 hr | 2 hr | 4 hr | 8 hr | 12 hr | 24 hr | All

| | Radiology-PET-DCAM | | | | | | N08E | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 12/23 0700 - 12/24 0659 | | | | | | | 12/24 0700 - 12/25 0659 | | | | | |
| Time: | 1700 | 1702 | 1732 | 1755 | 2059 | 2146 | 0624 | 0801 | 0908 | 1114 | 1346 | 1347 | |
| **Glucose (mg/dL)** | Graphs cannot display in the current view | | | | | | | | | | | | |
| **Accucheck** | | | | | | | | | | | | | |
| POC Glucose | 52 | 46 | 104 | | 141 | | | 275 | | 257 | | | POC Glucose |
| **Serum Glucose** | | | | | | | | | | | | | |
| Serum Glucose | | | | | | | 260 | | | | | | Serum Gluc... |
| **Insulin Dose** | | | | | | | | | | | | | |
| INSULIN ASPART SUB... | | | | 10 | | | | | 16 | | 8 | 8 | INSULIN A... |
| INSULIN GLARGINE,H... | | | | | | 24 | | | | | | | INSULIN G... |

Lantus increased to 27U and novolog 8U TID CC

- Current A1c 9.3% (reported A1c 6-7%) previously
- BGs much higher since her other “problems” of “feeling off balance” started this past summer
- Requiring >60U insulin/day during this hospitalization

**11/29/2016 7:40 AM - Lab Interface**

**Component Results**

| Component | Value | Ref Range & Units | Status |
|---|---|---|---|
| **GAD65 Ab Assay** | **1401 (H)** | <=0.02 nmol/L | Final |
| Comment: | | | |

**11/29/2016 7:40 AM - Lab Interface**

**Component Results**

| Component | Value | Ref Range & Units | Status |
|---|---|---|---|
| **GAD65 Ab Assay** | **1401 (H)** | <=0.02 nmol/L | Final |
| Comment: | | | |

- Received IVIG (2g/kg total divided in 5 days) during hospitalization

- Recommended obtaining islet cell antibody & ZnT8 Abs; these were not ordered by Primary team

**11/29/2016 7:40 AM - Lab Interface**

**Component Results**

| Component | Value | Ref Range & Units | Status |
|---|---|---|---|
| **GAD65 Ab Assay** | **1401 (H)** | <=0.02 nmol/L | Final |
| Comment: | | | |

**12/29/2016 3:24 PM - Lab Interface**

**Component Results**

| Component | Value | Ref Range & Units | Status |
|---|---|---|---|
| **GAD65 Ab Assay** | **704 (H)** | <=0.02 nmol/L | Final |
| Comment: | | | |

**11/29/2016 7:40 AM - Lab Interface**

**Component Results**

| Component | Value | Ref Range & Units | Status |
|---|---|---|---|
| **GAD65 Ab Assay** | **1401 (H)** | <=0.02 nmol/L | Final |
| Comment: | | | |

**12/29/2016 3:24 PM - Lab Interface**

**Component Results**

| Component | Value | Ref Range & Units | Status |
|---|---|---|---|
| **GAD65 Ab Assay** | **704 (H)** | <=0.02 nmol/L | Final |
| Comment: | | | |

- Gad65 antibody titer decreased after IVIG treatment

# GAD65

- Glutamic acid decarboxylase (GAD) is the rate limiting enzyme for the production of GABA (gamma aminobutyric acid), the main inhibitory neurotransmitter in the CNS

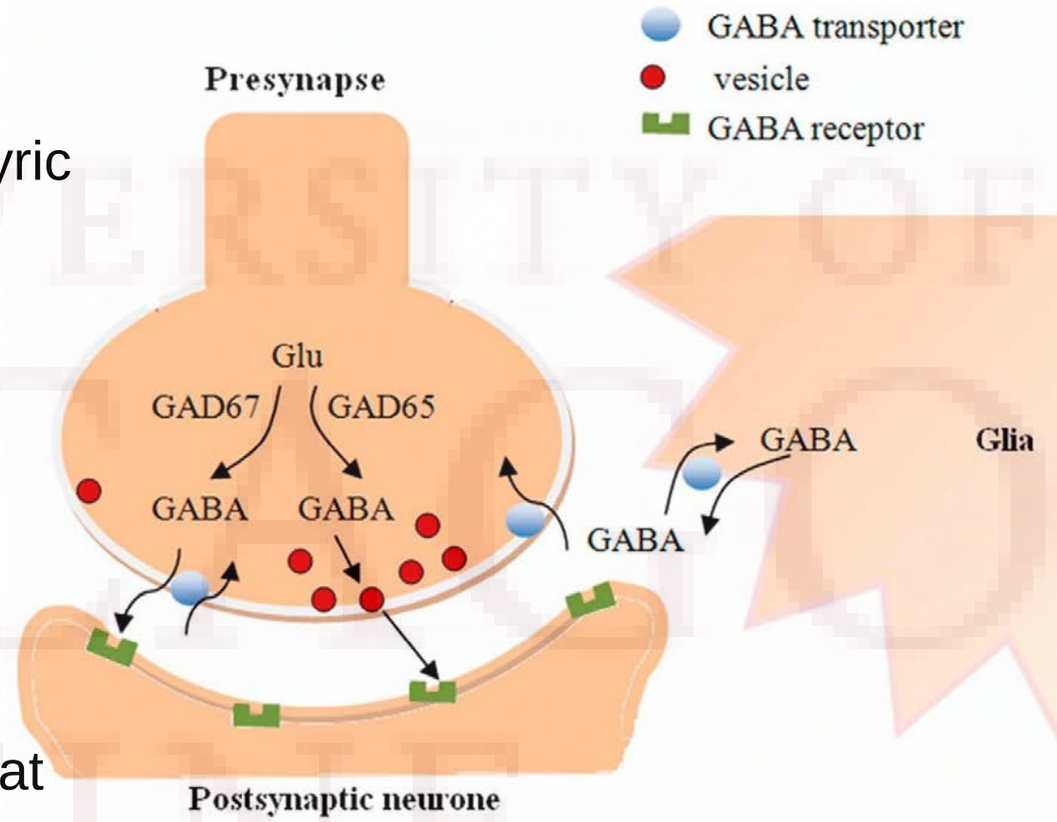
- GAD is expressed in CNS GABAergic neurons & in pancreatic islet beta cells

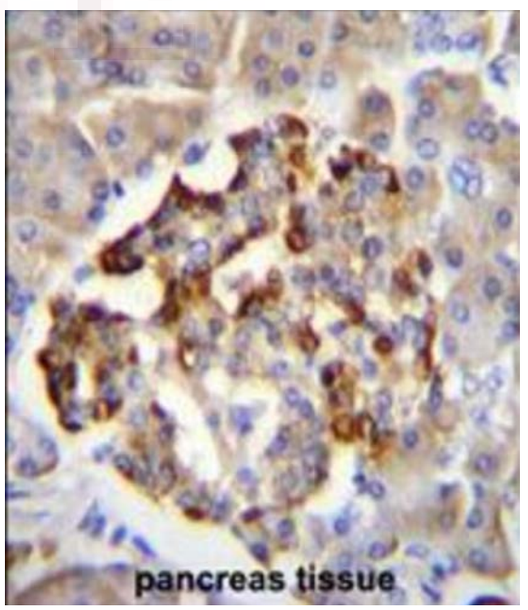
- GAD exists as two isoforms: GAD65 & GAD67

  - GAD65 is associated with the CM at the nerve terminals, involved GABA synthesis & its exocytosis at inhibitory synapses

  - GAD67 is mainly expressed in the cytoplasm of neurons; thought to regulate basal levels of GABA

- Anti-GAD65 Abs were first described in T1DM and are considered a biological marker of this disease




GAD65 staining by IH

# GAD65

- Antibodies to GAD65 are associated with several diseases including T1DM (80% of new onset Pts), Stiff Person Syndrome (60-80% of Pts), cerebellar ataxia (30-60%), intractable epilepsy, & Batten disease

- GAD65 Ab in Pts with neurological disease is typically 100-fold higher compared to Pts with T1D

- Gad65 Ab from its with neurological symptoms recognize both linear and conformational epitopes

- GAD65 Ab in T1D only recognize conformational epitopes

- Monoclonal GAD65Ab representing GAD65Ab specificities in neurological conditions lead to functional impairment of GABAergic synaptic transmission both *in vivo* & *in vitro* (not seen in T1D)

**Table 1**

The classification of immune-mediated cerebellar ataxias

| | |
|---|---|
| 1. Autoimmunity that mainly targets the cerebellum[a] or its related structures[b]: | |
| Cerebellar autoimmunity not triggered by another disease: | |
| Anti-GAD Abs associated cerebellar ataxia | |
| Cerebellar type of Hashimoto's encephalopathy | |
| Primary autoimmune cerebellar ataxia | |
| Others | |
| Cerebellar autoimmunity triggered by another disease or condition: | |
| Gluten ataxia | (gluten sensitivity) |
| Acute cerebellitis | (infection) |
| Miller Fisher syndrome | (infection) |
| Paraneoplastic cerebellar degenerations | (neoplasm) |
| 2. Autoimmunity that simultaneously targets various parts of the CNS: | |
| Multiple sclerosis | |
| Ataxia in the context of connective tissue diseases such as SLE | |

[a]When cerebellar ataxias are sole or main symptoms, the cerebellum is presumed to be the main target of autoimmunity

[b]For example, involvement of the proprioceptive spinocerebellar pathway is assumed in Miller Fisher syndrome

[c]Paraneoplastic patients are exceptional

# Cerebellar Ataxia (CA) with GAD-Ab

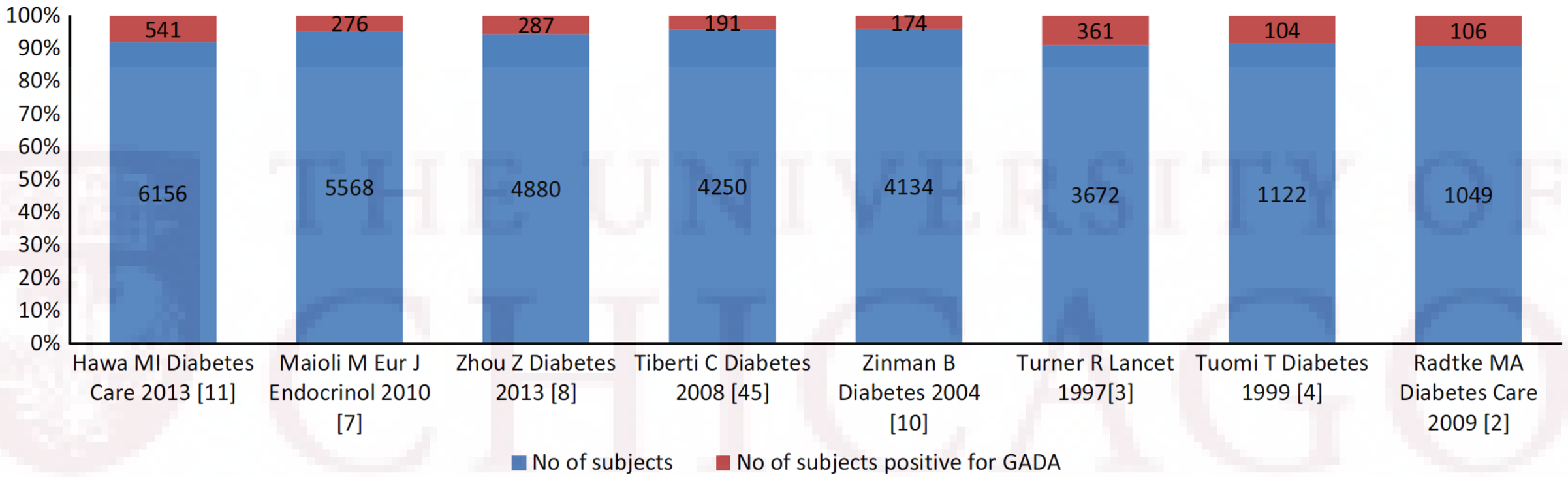
- Mostly affects women in their 6$^{th}$ decade
- CA installs either insidiously or subacutely & tends to progress continuously over time
- Symptoms include mainly static ataxia, dysarthria, and nystagmus
- CA may co-exist with SPS, peripheral neuropathy, limb stiffness, and MG
- Associated with PMH or FH of other autoimmune diseases such as T1DM, hemolytic anemia, or thyroiditis
- Poor prognosis with most patients remaining significantly disabled
- IVIG may have beneficial effect in some patients

# LADA

- Latent autoimmune diabetes of adults (LADA) thought of as slow onset TID or diabetes Type 1.5
- Adult onset, presence of diabetes associated autoantibodies & often with a slower course of onset not requiring insulin treatment for a period after diagnosis
- Diagnosis is based on elevated BGs with clinical impression of islet failure rather than insulin resistance
    - detection of low C-peptide and raised antibodies against pancreatic islets
    - Gad65 (most common), islet cell autoantibody, IA-1, ZnT8 should be performed

**Table 1** Diabetes classification

| Diabetes subtype | Type 1 | Adult-onset autoimmune diabetes: Latent autoimmune diabetes of adults | Adult-onset autoimmune diabetes: Autoimmune antibody-negative | Type 2 diabetes |
|---|---|---|---|---|
| Autoantibodies | Yes | Yes | No | No |
| Islet-reactive T cells | Yes | Yes | Yes | No |
| Insulin required at diagnosis | Yes | No | No | Variable |




Diabet Med. 32, 843-852 (2015)

# About 5-10% of patients classified with T2DM have GAD Abs

# Metabolic Features of LADA

- Patients with LADA require insulin more frequently and earlier post diagnosis than those with antibody negative T2DM
- GAD-Ab positivity in adult patients with non insulin requiring diabetes is associated with decreased fasting C peptide and decreased C peptide response to oral glucose
- Patients with LADA tend to have fewer signs of metabolic syndrome but higher A1c’s compared to T2DM
- Associated with less aggressive beta cell loss than childhood onset autoimmune DM, less HLA- associated genetic susceptibility & fewer multiple autoantibodies

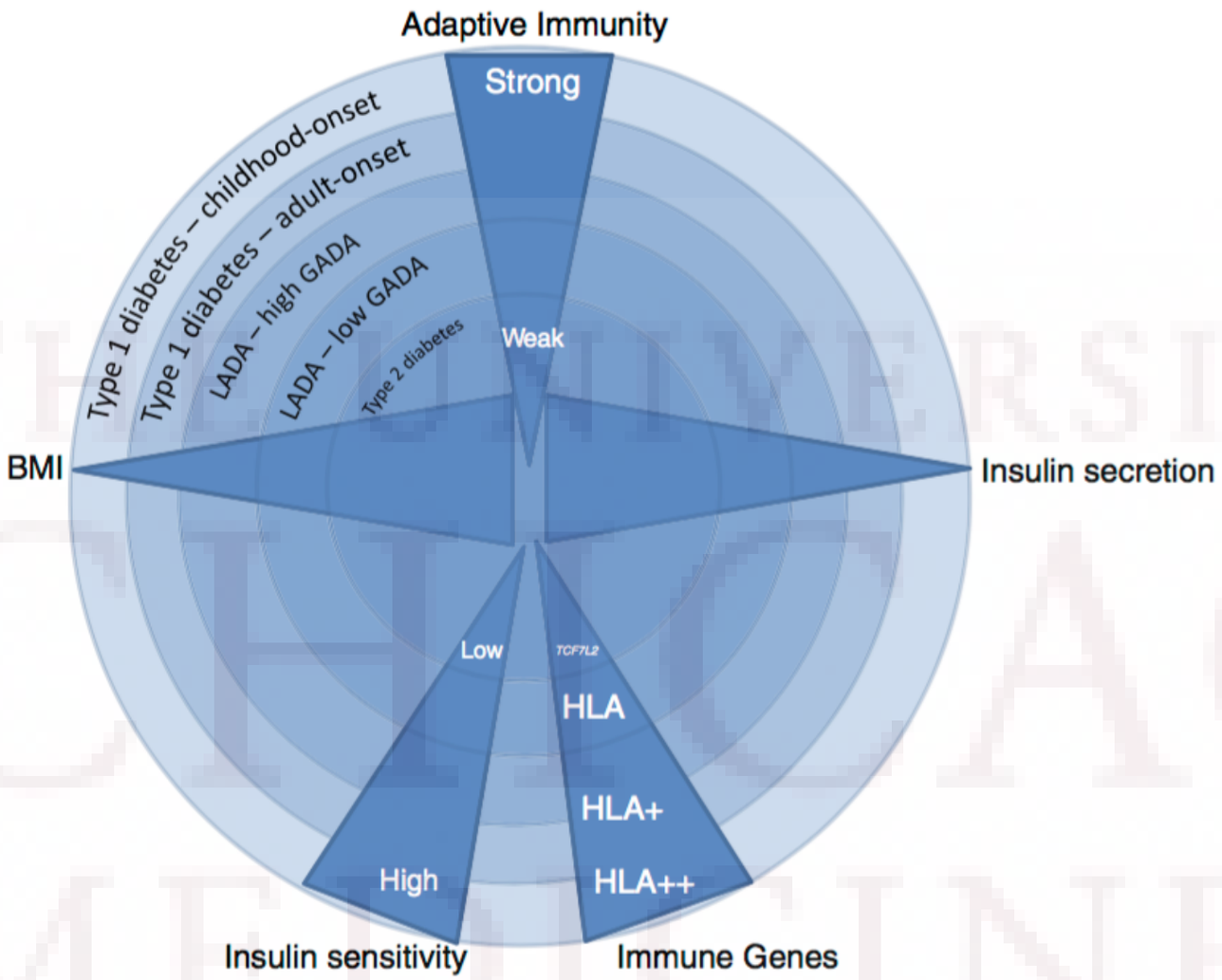



**Fig. 1** Homo diabeticus illustrating the continua of disease-associated factors across the range of diabetic phenotypes. Variable combinations of disease-associated characteristics are observed according to diabetes type for obesity (body mass index), influence of adaptive immunity and immune genes, and level of insulin secretion and insulin sensitivity. *BMI* body mass index, *LADA* latent autoimmune diabetes of the adult, *GADA* glutamic acid decarboxylase antibody, *HLA* human leukocyte antigen. To be validated: *TCF7L2*; transcription factor 7-like 2 gene

# Co-Morbidities with LADA

- Higher prevalence of autoimmune diseases, especially thyroid disease
- Monitoring thyroid function more closely and potentially screening for other autoimmune disease may be important in management

# Management Strategies in LADA

- No controlled studies on effect of metformin alone in LADA
- One study in Japan showed sulfonylureas worsened C peptide secretion; thus they should not be used in LADA
- One study in China supported the use of thiazolidinediones showing preservation of beta cell function; however, not widely used
- DPP4 inhibitors have been shown to reduce C peptide decline when given with glargine (versus glargine & placebo)

# Auto-immune cerebellar ataxia with anti-GAD antibodies accompanied by de novo late-onset type 1 diabetes mellitus - 24/09/08

*Ataxie cérébelleuse auto-immune avec anticorps anti-GAD et diabète de type 1 à début tardif*

Doi : 10.1016/j.diabet.2008.02.002

**C. Bayreuther [a, *], S. Hieronimus [b], P. Ferrari [c], P. Thomas [a], C. Lebrun [a]**

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**[b] Endocrinology and Diabetology Department, Archet Hospital, route St Antoine Ginestière, 06200 Nice, France**

**[c] Laboratory of Biochemistry, Pasteur Hospital, 30, voie Romaine, 06002 Nice, France**

- Case report: 47F with PMH vitiligo & Graves disease presented with late onset T1DM
- For two years had complained of progressive gait instability and oscillopsia
- MRI showed cerebellar atrophy
- Immunological staining positive for GAD65-Ab, TPO-Ab, TG Ab, 21-hydroxylase Ab, gastric parietal cell Ab & GM1 ganglioside; “auto-immune polyendocrinopathy”
- Symptoms improved with IVIG

# Continued course

- Pt readmitted a few weeks later with DKA
- Expressed confusion with insulin regimen
- Had been discharged with Lantus 27U and novolog 8U TID CC
- Transitioned off drip and discharged with same regimen
- CDE met with Pt extensively to go over regimen & distinguish between long and short acting insulin
- Unknown if Pt had LADA all along, or if this represents T2DM progressing to autoimmune diabetes in the setting of the development of GAD related autoimmune ataxia

# Conclusions

- LADA is associated with the same genetic & immunological features as child onset T1DM but also shares genetic features with T2DM

- GAD65 is an antibody biomarker of autoimmune CNS disorders (like cerebellar ataxia & stiff person syndrome) but more commonly, non-neurological autoimmune diseases (Type 1 DM, autoimmune thyroid disease)

- The progression of T2DM to LADA in the setting of GAD65 related ataxia has not previously been described

# References


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