A 55 year old with latent autoimmune diabetes and unsteady gait

Matt Ettleson, M.D.*

Endorama

December 3, 2020

*I have no relevant financial relationships with any commercial interests or other conflicts of interest.

AT THE FOREFRONT
UChicago Medicine

Learning Objectives

- Discuss the history of latent autoimmune diabetes of adulthood (LADA)
- Explore the relationship between a rare neurological disease and diabetes mellitus
- Review other musculoskeletal complications of diabetes mellitus

The endocrine consult service is called for a 53 year female patient with ‘insulin dependent diabetes’ with hyperglycemia who is admitted for recurrent nausea, vomiting, abdominal pain and 25 lb weight loss over last 3 months. Her inpatient glycemic management is currently complicated by a steroid prep for anticipated CT contrast studies to evaluate abdominal pain (because she has a history of contrast allergy).

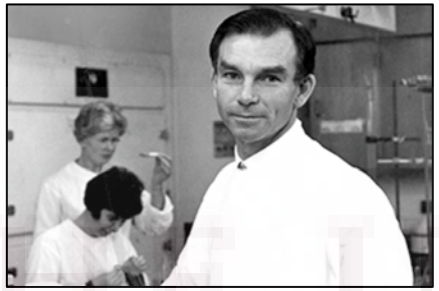
Regarding her history of diabetes…

- Diagnosed at 38 years of age with DKA (no records available)
- She has no family history of diabetes, mother with Addison’s disease
- She underwent pancreas transplant in 2004 and was off insulin for 7 years until transplant rejection in 2011
- She is currently on basal-bolus insulin at home (Levemir 26 units in split dose, novolog 8 units with meals)
- She has a history of multiple admission for DKA
- Her most recent A1c is 9.7
- no known retinopathy or nephropathy, does endorse symptoms consistent with peripheral neuropathy

Classification of diabetes?

May, 2015

Latent Autoimmune Diabetes of Adulthood



Rapid Publications

Antibodies to Glutamic Acid Decarboxylase Reveal Latent Autoimmune Diabetes Mellitus in Adults With a Non–Insulin-Dependent Onset of Disease

TIINAMAIJA TUOMI, LEIF C. GROOP, PAUL Z. ZIMMET, MERRILL J. ROWLEY, WILLIAM KNOWLES, AND IAN R. MACKAY

The classification of adults with diabetes mellitus can be invalidated by patients who initially present as NIDDM but who later become frankly insulin dependent. In some of these, the pathogenesis could be similar to that in IDDM, namely autoimmune destruction of the pancreatic β-cells. We studied 102 patients >35 yr of age at diabetes onset who had initially been nonketotic and non-insulin-dependent for ≥6 mo. They were classified according to glucagon-stimulated C-peptide levels into an insulin-deficient group (n = 33) and a non–insulin-deficient group (n = 69). We measured antibodies to GAD, islet cell cytoplasm, thyroid antigens, and gastric parietal cells in both groups. Anti-GAD was significantly higher in the insulin deficient group, 76% (25 of 33), than in the non–insulin deficient group, 12% (8 of 69), and this difference was substantially greater than that shown for ICAs. Thus, in a proportion of adults who present

In patients with adult-onset diabetes mellitus, the classification into IDDM or NIDDM categories may be difficult (1). It is estimated that, among patients with IDDM, 40% develop diabetes by 15 yr of age, 30% between 15 and 34 yr of age, and 30% thereafter. Also, annually, 1–2% with apparent NIDDM become insulin deficient (2). Most patients with NIDDM who eventually receive insulin have a relative rather than an absolute deficiency of insulin in that they cannot increase insulin secretion to compensate for their degree of insulin resistance (3). However, certain NIDDM patients develop an absolute insulin deficiency within a few years, the so-called type 1 1/2 diabetes (4) or latent IDDM (5). These patients have many features of classical IDDM: low C-peptide levels, low body-weight, ICAs, other organ-

study population:
- 102 Finnish adults
- diagnosed at 35+ years of age
- nonketotic diabetes
- without insulin use over last 6 months

methods:
insulin-dependent status was determined by measuring c-peptide after an overnight fast and 6 min after glucagon injection
(<0.6 nM = insulin deficient)

GAD autoantibodies determined via radioimmunoprecipitation assay

Diabetes. 1993 Feb; 42(2):359 – 362.

Latent Autoimmune Diabetes of Adulthood

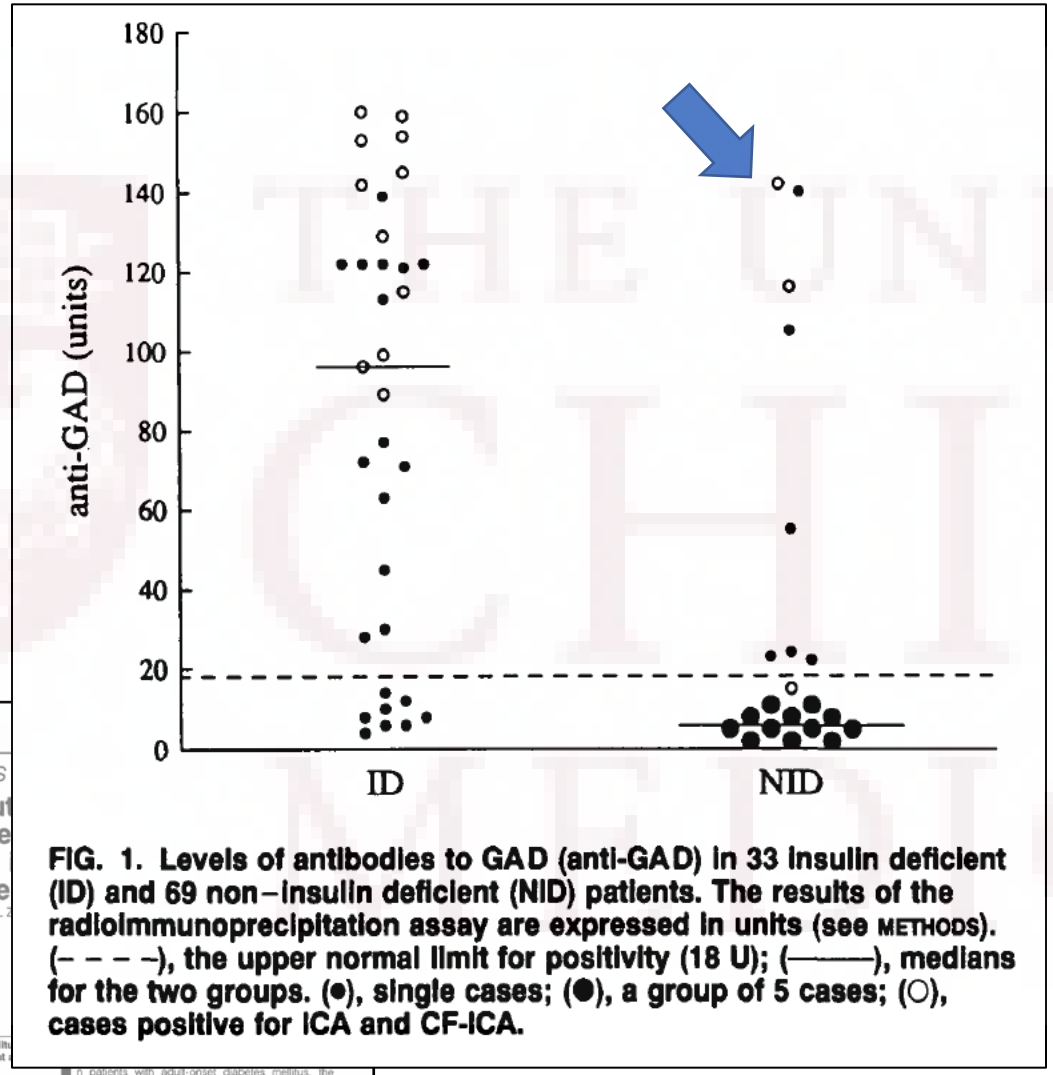


FIG. 1. Levels of antibodies to GAD (anti-GAD) in 33 insulin deficient (ID) and 69 non–insulin deficient (NID) patients. The results of the radioimmunoprecipitation assay are expressed in units (see METHODS). (– – – –), the upper normal limit for positivity (18 U); (———), medians for the two groups. (●), single cases; (⬤), a group of 5 cases; (○), cases positive for ICA and CF-ICA.

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Results:

	Insulin deficient	Non-insulin deficient	
GAD (+)	25	8	33
GAD (-)	8	61	69
	33	69	

Chi-square 41.99, p-value < 0.0001

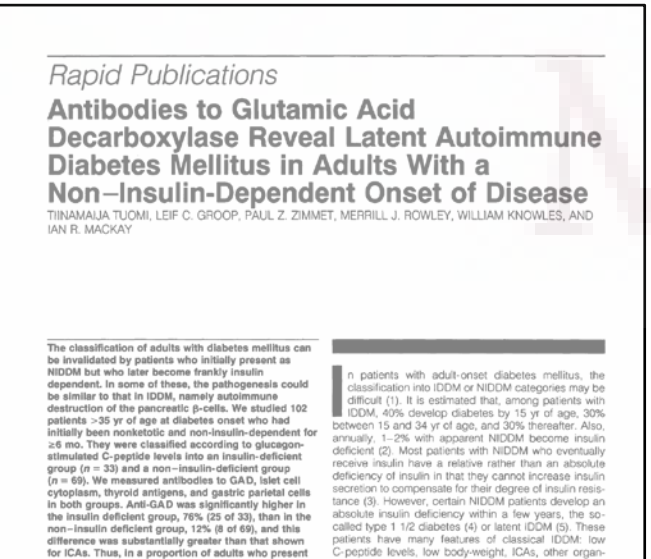
Odds ratio: 23.8, 95% CI: [7.2 - 81.8]

GAD (+) is highly associated with insulin deficiency.

GAD (+) was 76% sensitive and 88% specific in identifying insulin deficiency.

Latent Autoimmune Diabetes of Adulthood

The frequent finding of antibodies to GAD specifies a syndrome of LADA, and recognition of this has clear clinical implications. First, it further confirms that patients with LADA represent a discrete subgroup of IDDM with a pathogenesis similar to that of IDDM. Second, identification of this group at presentation would allow its subsequent exclusion in studies directed towards the pathogenesis of NIDDM. Third, given their strong probability of developing frank insulin deficiency, these patients should be followed more carefully to ensure prompt institution of insulin treatment, which may reduce various short- or long-term complications of diabetes, or even early treatment with immunosuppressive agents to halt the autoimmune process. Several studies already in progress are aimed at the prevention of diabetes in high-risk groups, e.g., ICA$^+$ siblings of IDDM patients. It would seem more appropriate to assess initially such treatment in LADA to determine whether residual β-cell function can be preserved.



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Latent Autoimmune Diabetes of Adulthood: definition, demographics and clinical characteristics

SPECIAL FEATURE

Review

Latent Autoimmune Diabetes in Adults

Ramachandra G. Naik, Barbara M. Brooks-Worrell, and Jerry P. Palmer

Charles River Clinical Services Northwest (R.G.N.), Tacoma, Washington 98418; and Department of Medicine (B.M.B.-W., J.P.P.), Division of Endocrinology, Metabolism, and Nutrition, Department of Veterans Affairs Puget Sound Health Care System, University of Washington, Seattle, Washington 98108

Context: Autoantibodies that are reactive to islet antigens are present at the time of diagnosis in most patients with type 1 diabetes. Additionally, approximately 10% of phenotypic type 2 diabetic patients are positive for at least one of the islet autoantibodies, and this group is often referred to as "latent autoimmune diabetes in adults (LADA)." These patients share many genetic and immunological similarities with type 1 diabetes, suggesting that LADA, like type 1 diabetes, is an autoimmune disease. However, there are differences in autoantibody clustering, T cell reactivity, and genetic susceptibility and protection between type 1 diabetes and LADA, implying important differences in the underlying disease processes.

Evidence Acquisition and Synthesis: In this clinical review, we will summarize the current understanding of LADA based on the MEDLINE search of all peer-reviewed publications (original articles and reviews) on this topic between 1974 and 2009.

Conclusions: In LADA, diabetes occurs earlier in the β-cell-destructive process because of the greater insulin resistance. Complexities arise also because of variable definitions of LADA and type 1 diabetes in adults. As immunomodulatory therapies that slow or halt the type 1 diabetes disease process are discovered, testing these therapies in LADA will be essential. (*J Clin Endocrinol Metab* 94: 4635–4644, 2009)

In clinical practice, the diagnosis of type 1 and type 2 diabetes is made using phenotypic characteristics such as age at onset, abruptness of onset of hyperglycemia, ketosis-proneness, degree of obesity (specifically central and intraabdominal), prevalence of other autoimmune diseases, and need for insulin replacement therapy. However, this clinical distinction is not always perfect (1, 2). The presence of genetic (3), immunological (4), and functional complexities (5) limits our ability to distinguish the type 1 *vs.* the type 2 disease processes. The disease process in classic type 1 patients is believed to be autoimmune in nature, whereas the disease process in classic type 2 is not autoimmune (6–8). However, there is increasing clinical evidence that highlights significant overlap between type 1 and type 2 diabetes, and the classification of diabetes into two main types has been challenged.

Discovery of islet cell antibodies in 1974 in the sera of subjects with type 1 diabetes provided very strong evidence that the β-cell lesion of type 1 diabetes was autoimmune in nature (9, 10); autoimmune β-cell dysfunction and destruction leads to insulin deficiency and generation of autoantibodies in the circulation, such as autoantibodies to islet-cell cytoplasm (ICA), and/or to glutamic acid decarboxylase 65 (GAD65; anti-GAD), and/or to the intracytoplasmatic domain of the tyrosine phosphatase-like protein IA-2 (IA-2A). Because there are no reliable markers for type 2 diabetes, absence of markers and/or manifestations of type 1 diabetes is often taken as indicating type 2 diabetes.

It was demonstrated by Irvine *et al.* (11) that about 11% of subjects with type 2 diabetes were also positive for ICAs. Compared with ICA-negative (ICA^-) type 2 diabetes, this ICA-positive (ICA^+) subset of type 2 diabetes subjects tended to fail sulfonylurea therapy and needed insulin treatment earlier (11). Similar subsets of phenotypic type 2 diabetes subjects who are positive for the antibodies

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2009-1120 Received June 11, 2009. Accepted September 9, 2009.
First Published Online October 16, 2009

Abbreviations: BMI, Body mass index; GAD, glutamic acid decarboxylase; HLA, histocompatibility leukocyte antigen; IAA, insulin autoantibodies; ICA, islet-cell cytoplasm; LADA, latent autoimmune diabetes of adults; ZnT8, zinc transporter.

- LADA may account for up to 12% of all cases of diabetes in some populations
- typical features include age >35 years, non-obese, and progression from diet-controlled disease to insulin-dependence is on the order of months to years
- weight loss, ketone proneness and low C-peptide
- In general, the presence of at least one antibody supports the diagnosis of LADA (islet cell, GAD65, IA-2, insulin, ZnT8)

J Clin Endocrinol Metab, Dec 2009, 94(12):4635 - 4644

Latent Autoimmune Diabetes of Adulthood: antibody positivity

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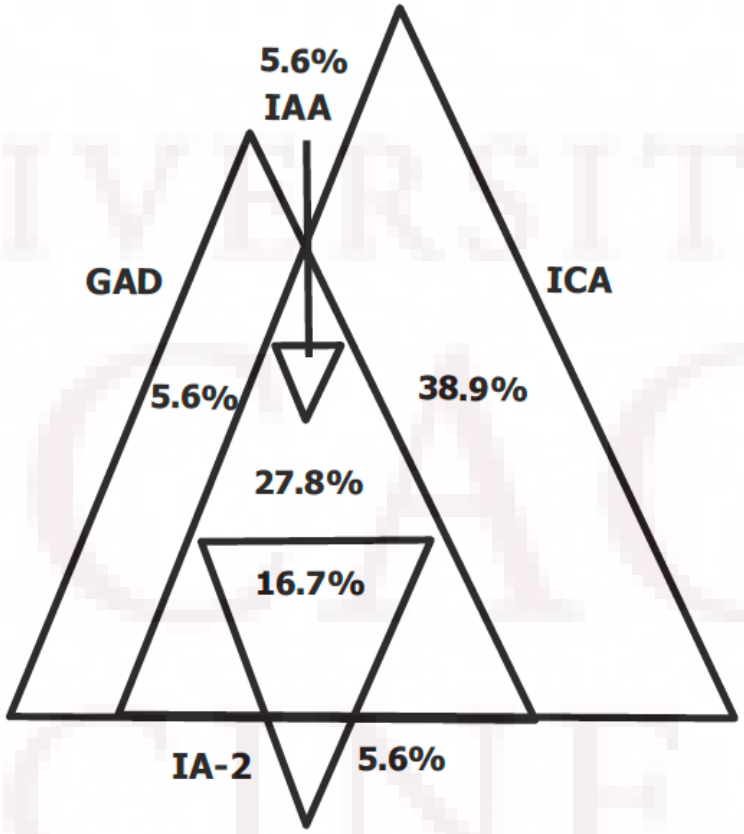

FIG. 1. Clustering of autoantibodies in autoantibody-positive patients. Numbers (%) refer to the percentage of the antibody-positive patients who were positive for the respective antibodies. [Reproduced with permission from R. Juneja *et al.*: *Metabolism* 50: 1008–1013, 2001 (18).]

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Latent Autoimmune Diabetes of Adulthood: genetics

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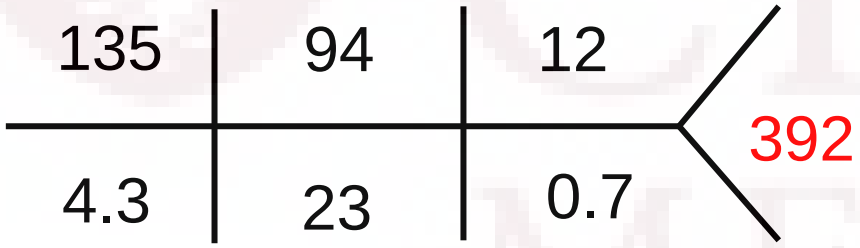
- LADA patients appear to have increased frequency of HLA alleles associated with susceptibility to type 1 DM
- However, protective HLA alleles (DR2 and DQβ1*0602) are more frequent in LADA patients vs those with type I DM
- Based on polymorphism studies, patients with LADA appear to share genetic determinants common to both type I and type 2 DM
- Family history of DM is a risk factor for the development of LADA

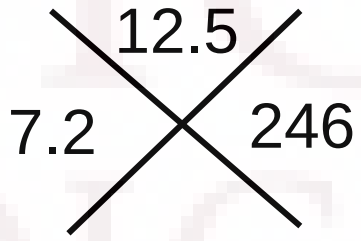
Back to the case…

J Clin Endocrinol Metab, Dec 2009, 94(12):4635 - 4644

Physical exam and laboratory results:

No acute distress. Thin and generally well appearing.
BP 137/88. HR 71. Temp 36.3. BMI 15.2.
Neck: supple, no thyromegaly
CV: regular rate and rhythm
Chest: clear to auscultation bilaterally
Abdomen: mild tenderness diffusely, no violaceous striae
Neuro: grossly intact
Skin: no lipo-hypertrophy or abdomen or lateral thighs
Foot exam: dry, but no sores/wounds





Cholesterol: 152
LDL: 79
HDL: 61
TGs: 58

Calcium: 9.3
Liver function tests unremarkable except for an ALT of 36
TSH: 0.67
HbA1c: 9.7

Discharge Summary

- improved symptoms with small frequent meals and reglan
- s/p TIPS revision (chronic portal vein thrombosis)
- Minimally delayed gastric emptying
- Insulin regimen adjusted to 12 units of Lantus daily and 1:20 ICR and a ISF 75 correctional scale
- Arrange for follow up at UC endocrinology clinic

Clinic follow up 2015 - 2017

- difficult to manage glycemic control, several admissions for DKA
- BMD in 2016 with -2.6 T score of total hip, started on denosumab, vitamin D supplementation
- Due to random low cortisol and ACTH during outside admission, underwent cosyntropin stim test: cortisol 18 → 24
  - clinic pituitary evaluation: cortisol 5.8, FSH 145, LH 43.4, IGF-1 99, TSH 1.22, FT4 1.23 (April 2017)
- Eventually lost to (endo) follow up by the end of 2017

The patient presents as an urgent consult to neurology clinic (Dr. Rezania) due to an acute onset of gait unsteadiness, dizziness and dysarthria. This was initially evaluated at her local hospital with an MRI, which reportedly did not show an area of acute ischemia or other abnormality. She is noted at this visit to have bilateral thigh pain for 2 months and toe/foot numbness. She was on gabapentin only at that time. She had a lower extremity NCV/EMG earlier in 2017 which was consistent with an axonal sensorimotor polyneuropathy and superimposed possible R lower lumbar radiculopathy.

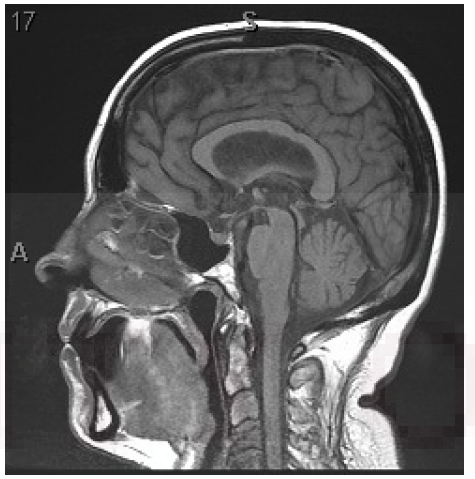
On physical examination:

- her speech is intact
- Cranial nerves are intact
- bilateral ptosis
- 5/5 strength in extremities bilaterally
- diminished pinprick and temperature to high shins and in distribution of R femoral nerve
- mild finger-nose-finger and heel-to-shin dysmetria and titubation (head nod)
- intermittent myoclonic movements in upper and lower extremities (spasms)

Exam suggests a possible cerebellar syndrome. Plan to admit for MRI and CSF studies.

June, 2017

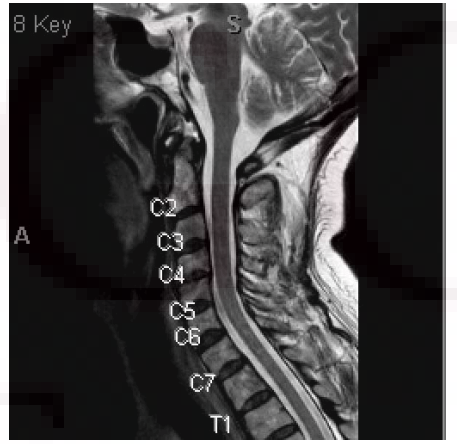
Brain MRI wo contrast



FINDINGS:

No evidence of diffusion restriction, edema or mass effect is seen. No significant focal parenchymal signal abnormality is identified. There is no evidence of intracranial hemorrhage or any abnormal extra-axial fluid collection. The ventricles are minimally prominent but still potentially within normal limits.

c-spine MRI wo contrast



FINDINGS:
The craniovertebral junction appears within normal limits. The cervical spine alignment is maintained and the cervical vertebral bodies and disc spaces are appropriate in height. The bone marrow signal is within normal limits. There is mild disc height loss and degenerative endplate changes involving the C4-5 level but no spinal canal or neuroforaminal stenosis is seen in the cervical spine. The cervical spinal cord has normal signal characteristics and overall morphology. The vertebral artery flow voids appear to be intact. The paraspinous soft tissue structures appear within normal limits.

CSF studies

3 WBCs, 1 RBC, 89% lymphocytes, glucose 134, protein 22, no oligoclonal bands, culture negative, ACE negative, neg paraneoplastic panel, infectious w/u negative

serum studies

HbA1c 12.0, neg paraneoplastic panel, ANA positive, dsDNA negative, ceruloplasmin normal, zinc normal, copper normal

GAD65 Ab: 3.07 nmol/L

ASSESSMENT & PLAN

 # Subacute symmetric persistent appendicular and trunkal ataxia accompanied by signs of brainstem deficit (right ptosis and dysarthria)
- Given symmetric presentation of symptoms, vascular lesion is low in the differential. Concomitant presence of brainstem signs, right ptosis and dysarthria and dysmetria points toward a more diffuse infratentorial process. Autoimmune cerebellitis remains on differential. History of myoclonus and pain may point towards Stiff-Man syndrome as well.
fter discussion with Dr. Rezania, patient continues to undergo IVIG as this has helped patient in the past.There is possibility that diabetic neuropathy may be confounding patient's ability to maintain steady gait and fluid motor movement, as patient's proprioceptive sense is likely compromised.

- IVIG x5 days, today is day 3/5. Increase to 800mg/kg per dose for patient for remaining therapy.
- MRI does not appear to explain above symptoms.
-Paraneoplastic panel negative
-Neurocheck q4h

Assessment & Plan

[redacted] is a **55Yrs** old **female** with PMHx significant for DM type I on insulin s/p pancreatic transplant in 2004 and failure in 2011, chronic abdominal pain, anxiety, malnutrition, and severe diabetic polyneuropathy who presents as follow up after a second hospital discharge for presumed autoimmune cerebellitis. She received 5 days of IVIG and states her symptoms have improved since discharge from the hospital, with some recurrence of symptoms since last week. Given the recurrent nature of her symptoms, I will recommend maintenance IVIG treatment (loading : 60 grams x 2 days, then 60 grams x1 day every month for 6 months) for her autoimmune ataxia/ she also has symptomatology suggestive for SPS during the episodes and has high GAD 65 titer (>x100 last titer). Her neurological exam on today's exam showed dysmetria in FNF and HTS tests, but the gait has dramatically improved compared to the last IVIG infusion, there is also evidence for length-dependent neuropathy which is stable.

Dr. Rezania

Linking stiff person syndrome (SPS) and diabetes through GAD autoimmunity

SPS essentials:

- progressive, fluctuating muscle rigidity of the limbs, trunk and neck
- EMG demonstrates continuous motor-unit activity at rest
- Associated with endocrine disorders: diabetes, hyperthyroidism, hypopituitarism

AUTOANTIBODIES TO GLUTAMIC ACID DECARBOXYLASE IN A PATIENT WITH STIFF-MAN SYNDROME, EPILEPSY, AND TYPE I DIABETES MELLITUS

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Abstract Stiff-man syndrome is a rare disorder of the central nervous system consisting of progressive, fluctuating muscle rigidity with painful spasms. It is occasionally associated with endocrine disorders, including insulin-dependent diabetes, and with epilepsy. We investigated the possible existence of autoimmunity against the nervous system in a patient with stiff-man syndrome associated with epilepsy and Type I diabetes mellitus.

Levels of IgG, which had an oligoclonal pattern, were elevated in the cerebrospinal fluid. The serum and the cerebrospinal fluid produced an identical, intense staining of all gray-matter regions when used to stain brain sections according to an indirect light-microscopical immunocytochemical procedure. The staining patterns were identical to those produced by antibodies to glutamic acid decarboxylase (the enzyme responsible for the synthesis of gamma-aminobutyric acid). A band comigrating with glutamic acid decarboxylase in sodium dodecyl sulfate–polyacrylamide gels appeared to be the only nervous-tissue antigen recognized by cerebrospinal fluid antibodies, and the predominant antigen recognized by serum antibodies.

These findings support the idea that an impairment of neuronal pathways that operate through gamma-aminobutyric acid is involved in the pathogenesis of stiff-man syndrome, and they raise the possibility of an autoimmune pathogenesis. (N Engl J Med 1988; 318: 1012-20.)

STIFF-MAN SYNDROME is a very rare disorder of the central nervous system, characterized by progressive and fluctuating muscle rigidity with superimposed painful spasms. The latter may occur spontaneously or be precipitated by sensory stimuli. The disease involves the muscles of the limbs, trunk, and neck, sometimes asymmetrically.[1,2] The diagnosis is established by the finding of a characteristic electromyographic pattern indicating continuous normal motor-unit activity at rest. Such activity is abolished by sleep, general or spinal anesthesia, peripheral-nerve blockade, curare, and intravenous diazepam.[2] The syndrome was first described by Moersch and Woltman in 1956,[1] and several reports of sporadic cases have been presented since then. Stiff-man syndrome has been reported to be associated with endocrine disorders — namely, diabetes mellitus,[3-5] hyperthyroidism,[6] and hypopituitarism[7] — and with epilepsy in about 10 percent of cases.[8,9]

The pathogenesis of the disorder is still debated. Clinical and pharmacologic evidence suggests that the continuous alpha motor-unit activity is due to an impairment of the suprasegmental or spinal inhibitory systems that operate through gamma-aminobutyric acid (GABA) (i.e., GABA-ergic inhibitory systems).[3,10]

The present report describes a typical case of stiff-man syndrome associated with epilepsy and Type I diabetes, in which autoantibodies directed against a major antigen of GABA-ergic cells were present. A preliminary account of this work has been published in abstract form.[11]

Case Report

A 49-year-old woman with a normal family medical history had a normal personal medical history until she was 39, when she underwent hysterectomy and bilateral ovariectomy because of uterine fibromyoma. During the same year she began to have grand mal seizures, facial vasomotor phenomena, and painful permanent contractures of the lumbar muscles, which caused marked hyperlordosis. Epilepsy associated with psychogenic contractures was diagnosed and treated with phenobarbital (100 mg per day). In the following years, the contractures spread progressively to the lower

A 39 year old woman began experiencing grand mal seizures and permanent contractures of the lumbar muscles in the months following hysterectomy for uterine fibromyoma. She responded well to diazepam for the contractures.

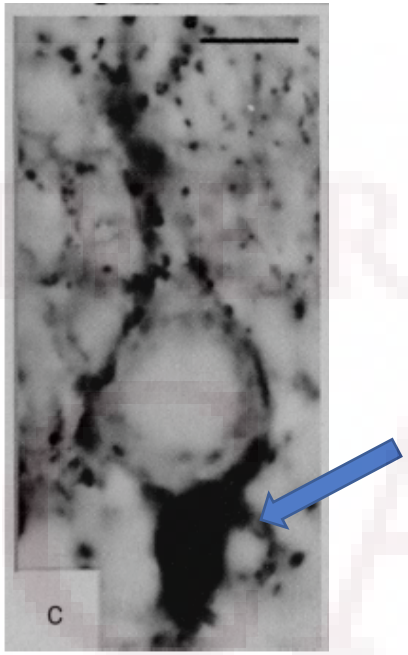
She presented again at age 48 with ketoacidotic coma after several weeks of polyuria and polydipsia.

Signs of autoimmunity against the CNS were investigated.

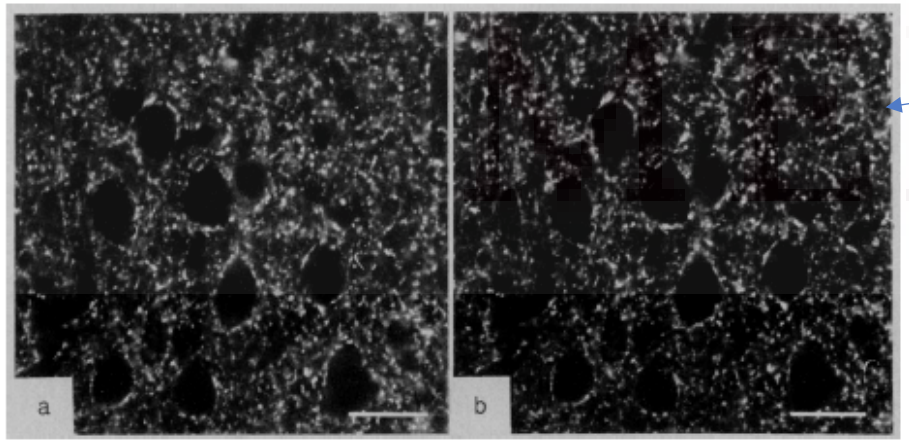
N Engl J Med. 1988 Apr 21:318(16):1012-20.

Linking stiff person syndrome (SPS) and diabetes through GAD autoimmunity

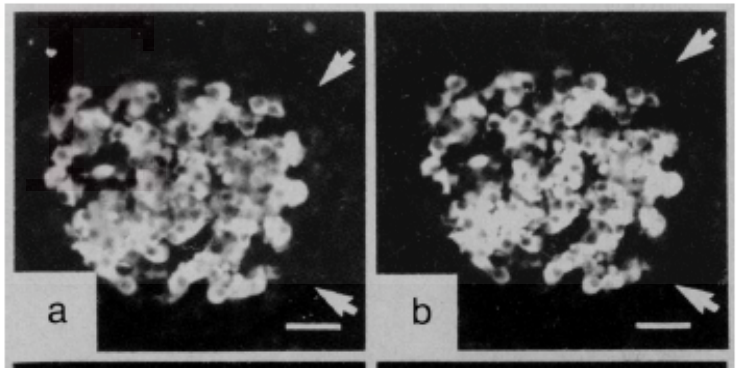
Samples of the patient's serum and cerebrospinal fluid were used to immunostain frozen sections of brain tissue.



Prominent activity was noted in the peripheral terminals of the cerebellar glomeruli, which are GABA-ergic.



The staining pattern in cerebral and pancreatic islet tissue produced by GAD antiserum was identical to that produced by the serum and CSF of the patient.



N Engl J Med. 1988 Apr 21:318(16):1012-20.

Hospital Course

- MRI brain and c-spine without evidence of inflammation
- CSF studies unrevealing for etiology
- under presumptive diagnosis of acute autoimmune cerebellitis, the patient received IVIG treatment with improvement in symptoms
- Follow up scheduled in neurology clinic

Clinic follow up 2017 - present

- based on GAD65 antibody positivity, improvement in neurological symptoms with IVIG treatment and lack of alternative diagnoses, presumptive diagnosis of SPS made
- patient eventually started on insulin pump therapy with improvement in glycemic control (outside endo clinic)

Admission 9/2020 for IVIG and PLEX therapy

- admitted for acute worsening of gait ataxia
- HbA1c 6.7 on admission
- PLEX therapy complicated by thrombosis of central line, but symptoms improved
- Continues on IVIG therapy every 3 weeks

Date	8/25/16	6/7/17	11/21/17	2/13/18	4/6/18	10/30/18	9/27/20
GAD65 (nmol/L)	2.96	3.07		2.33	3.53	0.41	0.26
HbA1c (%)	9.0	12.0	12.6				6.7

IVIG therapy started

treated with baclofen, diazepam and gabapentin

SPS: an overview

Does this patient have stiff-person syndrome?

Diagnostic criteria

Major criteria

1. Stiffness in axial and limb muscles, prominently in paraspinal muscles
2. Superimposed muscle spasms, often precipitated by sensory stimuli
3. EMG: continuous motor unit activity
4. Absence of other neurological disorders that could explain symptoms

Minor criteria

5. Positive serum anti-GAD65 antibodies
6. Clinical improvement with benzodiazepines

Subtypes

Classic SPS

Paraneoplastic SPS

SPS variants

includes SPS plus (ataxia, epilepsy, etc)

J Neurol Neurosurg Psychiatry. 2015 Aug;86(8):840-848.

SPS: an overview

Associated autoimmune disorders	Associated neoplasia
Diabetes mellitus type 1 ★	Breast cancer‡
Hashimoto's thyroiditis ★	Pulmonary cancer
Grave's disease ★	Renal cell carcinoma
Pernicious anemia	Thyroid carcinoma ★
Anti-NMDAR encephalitis	Colon cancer
Limbic encephalitis	Neuroendocrine neoplasm ★
Refractory epilepsy	Thymoma
Polyendocrine autoimmune syndrome ★	Hodgkin lymphoma
Vitiligo	Non-Hodgkin lymphoma
Caeliac disease	Cholangiocarcinoma
Myasthenia gravis	
Autoimmune retinopathy and scleritis	
Systemic lupus erythematosus	

★ endocrine-related disorders

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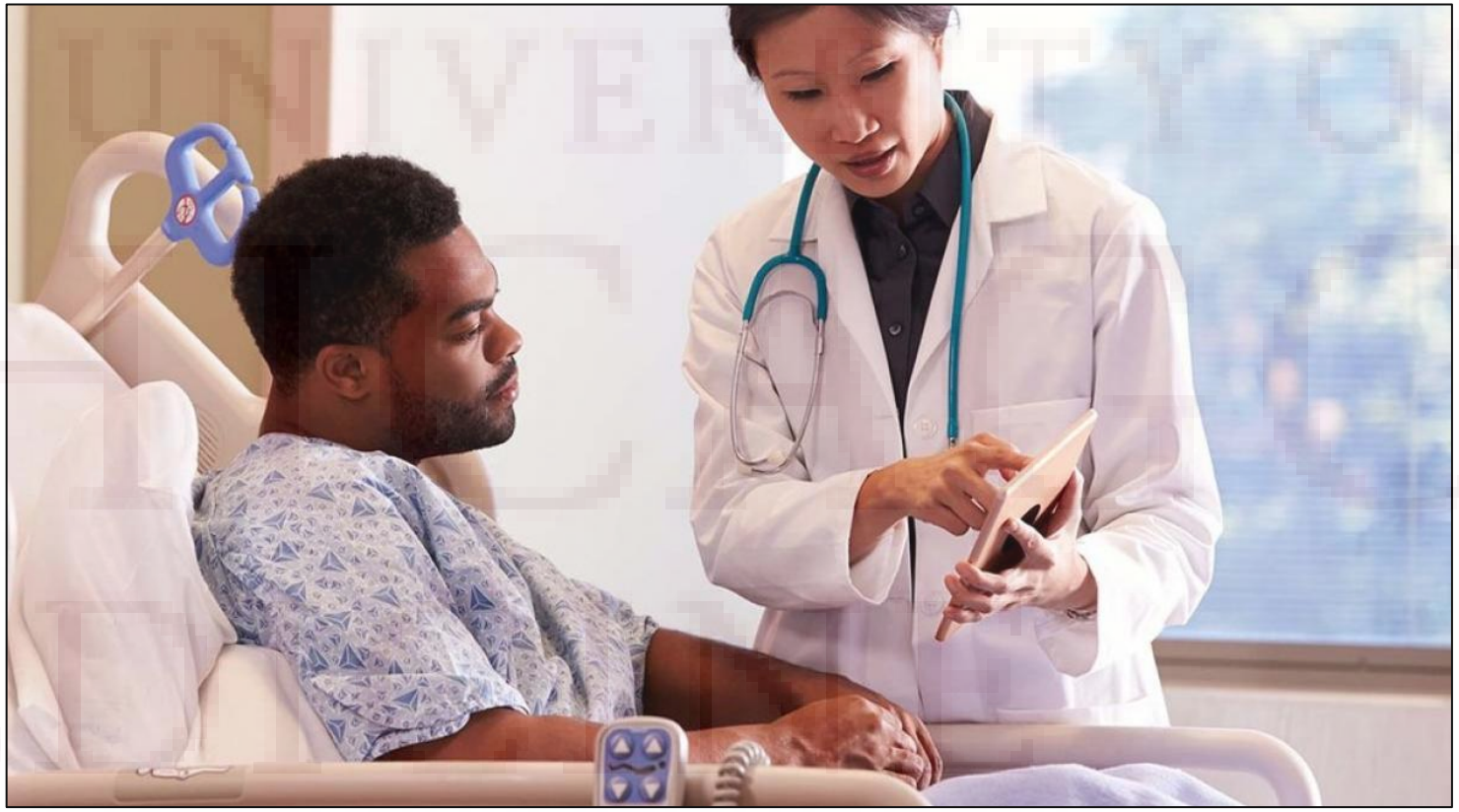
SPS: an overview

Recommended treatments include:

- Benzodiazepines
- Anti-epileptics
- Baclofen
- Dantrolene
- Botox
- immunotherapy
  - Corticosteroids
  - IVIG
  - Rituximab
  - Plasma exchange
  - tacrolimus
  - mycophenolate
  - …



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LADA and SPS: a spectrum of phenotypes?

Case 1: 6 month history of R leg stiffness, foot spasms and pain
Cast 2: episodic brief truncal and lower-limb spasms progressive over 20+ years

Table 1—Summary of LADA and SPS cases

	Case 1	Case 2
Age at diabetes diagnosis (years)	70	40
Age at SPS diagnosis (years)	72	78
Age at insulin requirement (years)	NA	42
HbA_{1c} at LADA diagnosis, % (mmol/mol)	7.8 (62)	6.8 (51)
GADA (units/mL) (ref. <5.0 units)	71	>2,000
Basal C-peptide (nmol/L)	0.34	<0.03
Glucagon-stimulated C-peptide (nmol/L)	0.62	<0.03
Class II HLA	DQ2,8	DQ2,8

insulin requirement developed over 2 years

relative insulin deficiency

Shared genetic risk

Diabetes Care. 2014 Oct;37(10):e214-215.

More common musculoskeletal complications of diabetes

A potential theory linking diabetes and disorders like adhesive capsulitis is that advanced glycation end products act to crosslink collagen fibers, reducing mobility

Carpal tunnel syndrome: hand pain, paresthesia caused by compression of median nerve; type I and II DM appear to increase risk of disease by about 70%

Limited joint mobility: limited joint movement most often in the hands, but also in feet, ankles, shoulders; thickening of the skin on the dorsum of the hands may be present

Dupuytren's contracture: fibrosis of the palmar fascia leading to flexion contractures of the digits and nodule formation

Adhesive capsulitis (frozen shoulder): gradual development of global limitation of active and passive shoulder motion with no radiographic findings, including osteoarthritis

Neuropathic (Charcot) arthropathy: loss of sensation and poor vascularity leads to chronic, destructive arthropathy

Overview of the musculoskeletal complications of diabetes mellitus. Uptodate.com