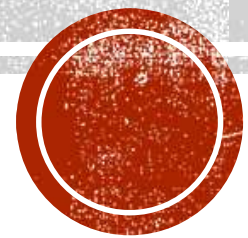
WHEN DIABETES IS NOT TYPE 2 OR TYPE 1

Tina kader frcp



DISCLOSURES

- Lectures
- Sanofi aventis; Medtronic; eli lilly; janssen ; astrazeneca; tandem; abbott
- Novonordisk; Bms
- Ad boards as above
- Research Sanofi; novonordisk

DIABETES IS MORE COMPLICATED WITH MANY DIFFERENT TYPES; EASY APPROACH

- Diabetes can be classified into the following general categories:
- Type 1 diabetes (due to autoimmune b-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
- Type 2 diabetes (due to a progressive loss of adequate b-cell insulin secretion frequently on the background of insulin resistance)
- Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
- Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

OBJECTIVES

- Understand other causes of diabetes
- Understand the meaning of monogenic diabetes
- Understand LADA; what is this and which patients should you screen
- Understand other diseases that can present with diabetes;

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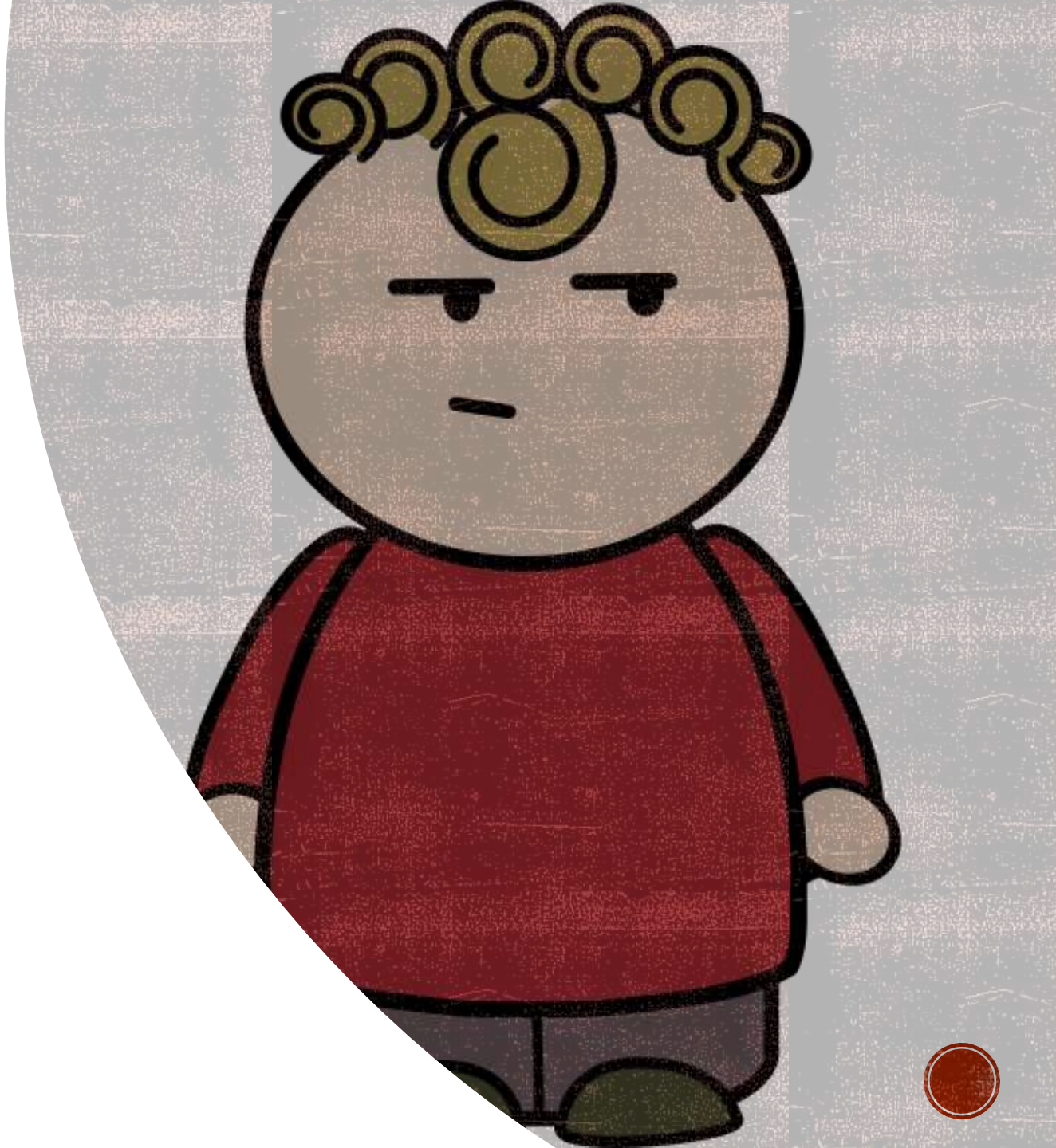
MODY

Maturity-**O**nset **D**iabetes of the **Y**oung

- In 1928, first noticed by Cammidge
- In 1975, first reported as MODY by Tattersall & Fajans ("Father of MODY")

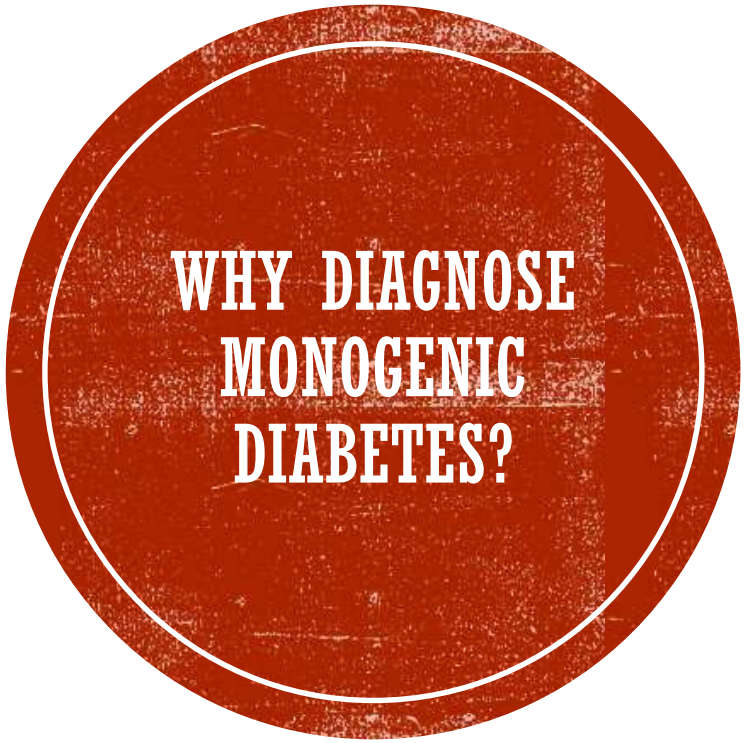
CASE 1

- Type 1 diabetes
- Diagnosed at age 12
- Interestingly had neonatal diabetes at birth one of the first cases at jgh
- Obese
- Poorly controlled a1c over 8
- Now 24
- Wants to know could she have another diagnosis



MONOGENIC DIABETES

- Inheritance of mutation in single gene
- Dominant ,recessive or denovo
- Most are due to mutations in genes which regulate βcell function
- Rare cases due to insulin resistance
- Can mimic type 1 or type 2 diabetes



To elucidate the pathophysiology

Changes the treatment

For example

- NO need of drugs- GCK mutations
- insulin injections being replaced by tablets (low dose in HNFα or high dose in potassium channel defects -Kir6.2 and SUR1)
- tablets in addition to insulin (metformin in
- insulin resistant syndromes)

WHEN TO SUSPECT?

- Diagnosis of type 1 may be wrong when
  - A diagnosis of diabetes before 6 months
  - Family history of diabetes with a parent affected
  - Evidence of endogenous insulin production outside the ‘honeymoon’ phase (after 3 years of diabetes)
  - When pancreatic islet autoantibodies are absent,especially if measured at diagnosis

ALWAYS LISTEN TO YOUR PATIENTS

- She brought an article to me; that neonatal diabetes
- May be associated with a gene that may respond to tx with medications
- I was skeptical
- Take a patient off insulin

DID MY RESEARCH CONTACTED HER PEDIATRIC ENDO

- Sure enough she had a gene that encoded for monogenic diabetes
- Stopped insulin gradually
- Started diabeta
- Now 10 years later
- Lost 50 lbs
- A1c 0.066

SUMMARY

- Consider monogenic diabetes in young patients /those not fitting the original diagnosis
- Molecular testing available free for some-but careful patient selection is the key
- Diagnosing monogenic DM can free the patient from “shots”
- It is also cost effective to the system

Mechanism of Beta-cell dysfunction	Gene/Mutation
Reduced Beta-cell number Pancreatic aplasia	IPF1 homozygous PTF1A HNF1B
Reduced B-cell development Reduced metabolism Reduced glucose sensing Reduced metabolism	GCK Mitochondrial mutations HNF1A HNF1B HNF4A IPF1 heterozygous
Failure to depolarize membrane Failure to close K_{ATP} channel	KCNJ11 ABCC8
Increased destruction of B-cells Immune-mediated destruction Endoplasmic reticulum stress Increased apoptosis cause uncertain	FOXP3 INS EIF2AK3 WFS1 HNF1A HNF4A Mitochondrial mutations

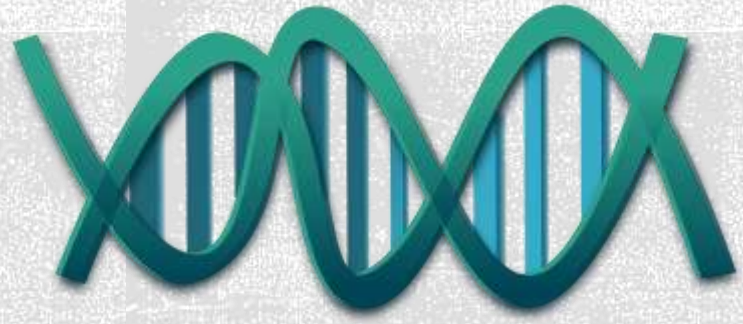


Table 2.6—Most common causes of monogenic diabetes (133)

	Gene	Inheritance	Clinical features
MODY	*GCK*	AD	GCK-MODY: stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
	HNF1A	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
Neonatal diabetes	*KCNJ11*	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (*PLAGL1*, *HYMA1*)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	EIF2B1	AD	Permanent diabetes: can be associated with fluctuating liver function (138)
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy; enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

WHEN TO SUSPECT?

1. Neonatal diabetes and diabetes diagnosed within the first 6 months of life
2. Familial diabetes with an affected parent
3. Mild (5.5–8.5 mmol/l) fasting hyperglycaemia especially if young or familial
4. Diabetes associated with extra pancreatic features

MONOGENIC DIABETES

- 35 year old followed by another endocrinologist
- Diagnosed with type 2
- On metformin
- Trying to get pregnant
- Renal cysts; liver abnormalities; low magnesium
- how to tie this all together
- Monogenic diabetes
- Be alert for this diagnosis; lean; family history; negative antibodies

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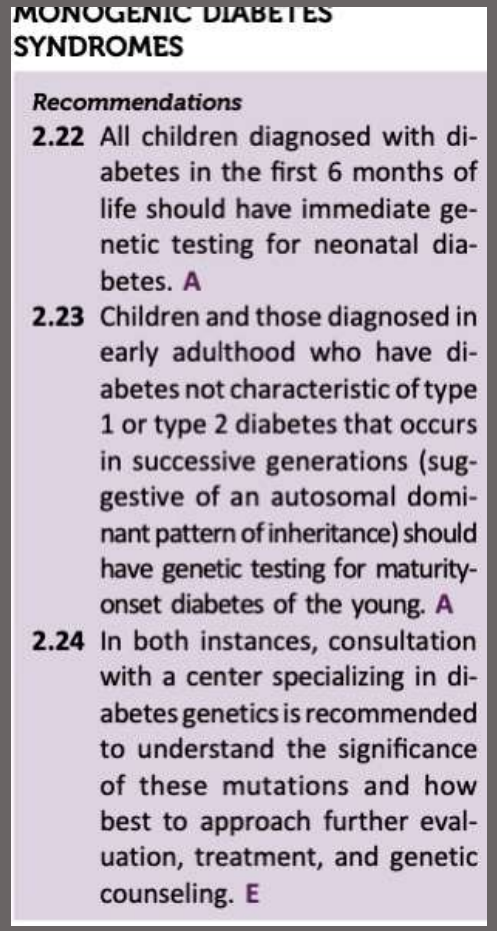

MONOGENIC DIABETES SYNDROMES

Recommendations

2.22 All children diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. A

2.23 Children and those diagnosed in early adulthood who have diabetes not characteristic of type 1 or type 2 diabetes that occurs in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young. A

2.24 In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of these mutations and how best to approach further evaluation, treatment, and genetic counseling. E

TAKE HOME MESSAGE 1

- Think about it in your young patients
- Negative antibodies for type 1
- Family history positive; dominant fashion
- Extra pancreatic abnormalities

OBJECTIVES

- Understand other causes of diabetes
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- ***Understand LADA; what is this and which patients should you screen***
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LADA

- Definition
- Late onset autoimmune
- Think about it in slim type 2 diabetes
- family history autoimmunity
- Progression to insulin

CASE

- 50 year old
- Prediabetes for a few years
- hashimotos
- In summer 2021 fasting sugar a bit high 6.4
- A1c 0.062
- Declined metformin
- Followed diet
- 4 months later polyuria and polydipsia
- Sugar random 30
- A1c 10 percent

LADA

Table 1—Broad characteristics of LADA*

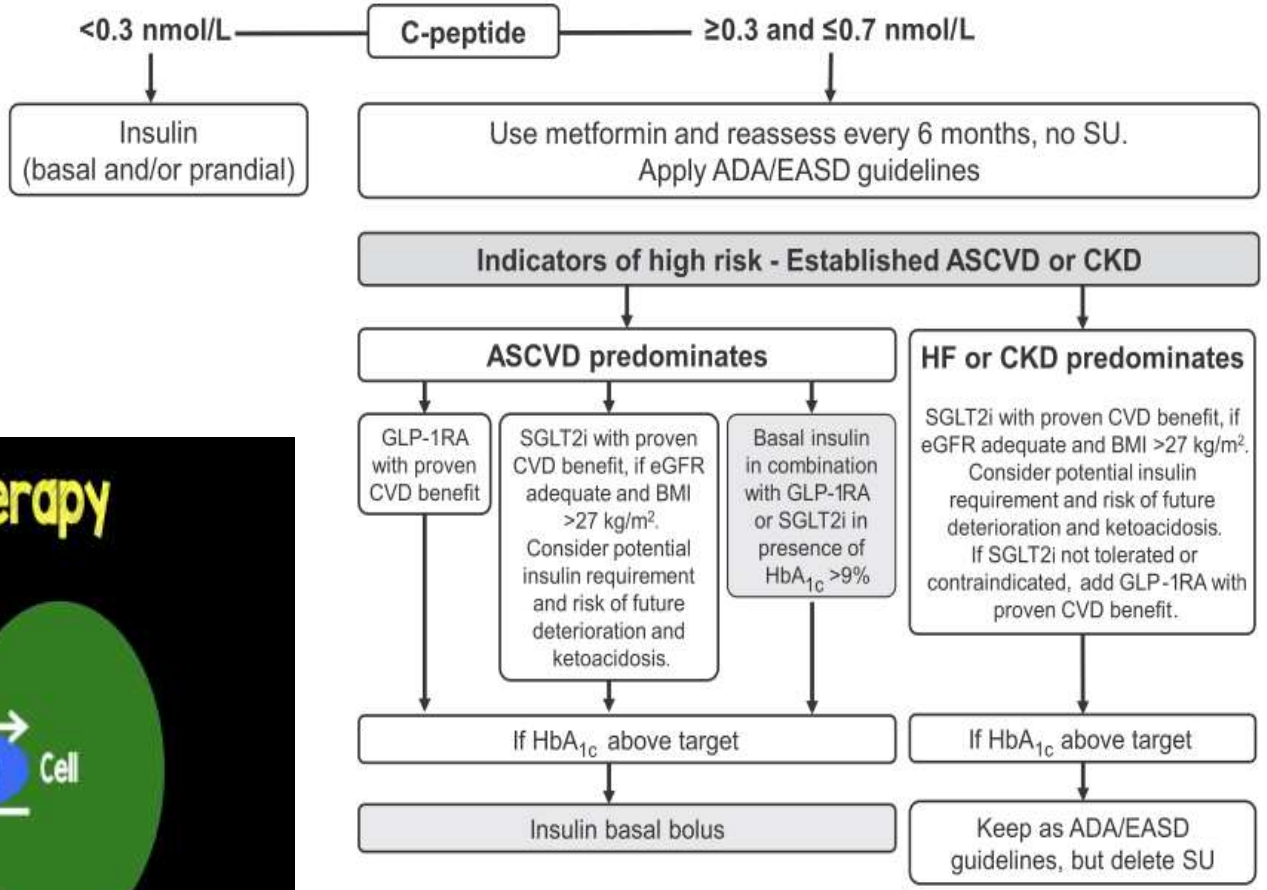
- Age >30 years**
- Family/personal history of autoimmunity
- Reduced frequency of metabolic syndrome compared with T2D—lower HOMA, lower BMI, lower blood pressure, and normal HDL compared with T2D
- No disease-specific difference in cardiovascular outcomes between these patients and those with T2D
- C-peptide levels decrease more slowly than in T1D
- Positivity for GADA as the most sensitive marker; other autoantibodies less frequent (ICA, IA-2A, ZnT8A, and tetraspanin 7 autoantibodies)
- Non–insulin requiring at onset of diabetes

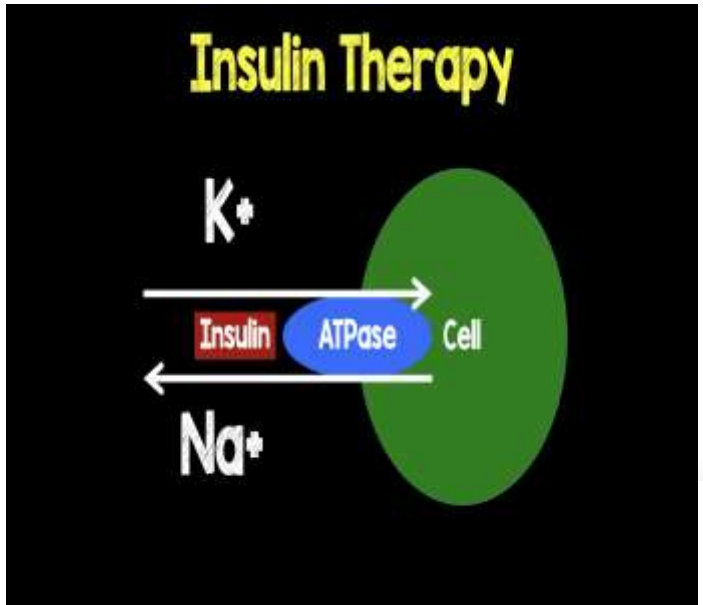
*None of these features categorically define LADA. **Limited data on older patients with higher probability of T1D in younger patients.

WAS ADMITTED

- Sent home on orals and basal
- cpeptide normal but low end
- Rapidly improved; even 4 units make her hypoglcyemic
- Had ordered antigad and cpeptide
- Insulin stop
- On glumetza and Jardiance
- Has Dexcom
- Normal sugars
- Aware of risk ketoacidosis

TREATMENT ALOGORITHMS





TAKE HOME MESSAGE 2

- LADA PATIENTS ARE IN YOUR PRACTISE
- THINK ABOUT THIS IF LEAN ; ORAL OR OTHER INJECTABLES NOT WORKING
- OTHER AUTOIMMUNE DISORDERS
- GET ANTIGAD AND CPEPTIDE
- AT RISK OF DKA IF CPEPTIDE GETS LOWER

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50 YEAR OLD TYPE 2

- NEW CASE
- 50 YEARS OLD
- TYPE 2 DM 15 YEARS
- CAROTID ARTERY DISEASE
- NO CAD
- INSULIN PUMP VICTOZA INVOKANA
- BASAL RATES 4 UNITS PER HOUR

EXAM

- CUSHINGOID
- SUPRACLAVICULAR FAT PADS
- MOON FACES TRIPLE CHINNED
- ABDOMINAL OBESITY
- NO STRIAE; NO PURPURA
- VERY MUSCULAR ARMS AND LEGS; SUPER ATHLETIC LOOKING
- LABS LDL 1.8
- A1C 0.067
- 24 HOUR CORTISOL NORMAL
- CT ABD NORMAL ADRENALS DONE FOR OTHER REASONS
- LFTS NORMAL
- TG MILDLY ELEVATED

PARTIAL LIPODYSTROPHY

- DUNIGANS
- CAN LEPTIN HELP

Inherited Lipodystrophies			
Type	**Salient features**	**Mode of inheritance**	**Genetic defects**
Congenital generalized lipodystrophy	Generalized deficiency of subcutaneous fat from birth	Autosomal recessive	AGPAT2, BSCL2, CAV1, PTRF, FBN1, BANF1
Familial partial lipodystrophy	Loss of subcutaneous fat from extremities with variable loss/excess of fat from trunk and face	Autosomal dominant (usually)	LMNA, PPARG, AKT2, PLIN1, CIDEC*
Lipodystrophy in association with other rare syndromes	Variable degree of fat loss in association with features of other syndromes such as MAD, SHORT, progeria and autoinflammatory syndromes	Both autosomal recessive and autosomal dominant	LMNA, ZMPSTE24, PSMB8, PIK3R1
Acquired Lipodystrophies			
Acquired generalized lipodystrophy	Development of generalized loss of subcutaneous fat, with normal fat distribution at birth		
Acquired partial lipodystrophy	Loss of subcutaneous fat from face, upper extremities and trunk, but not from lower extremities		
HIV-associated lipodystrophy	Loss of fat from face and limbs with variable loss/excess from trunk and associated with antiretroviral therapy		
Localized lipodystrophy	Patchy loss of subcutaneous fat usually following trauma or injections		

Abbreviations in the table: MAD, mandibuloacral dysplasia; SHORT, short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly and teething delay.

*CIDEC reported in a single patient with autosomal recessive inheritance.

OTHER DIAGNOSIS THAT CAN PRESENT WITH TYPE 2 DIABETES

- 60 year old male
- Come to my clinic in the states
- Type 2 diabetes followup
- On 3 ORAL AGENTS a1c 0.085
- Nothing really remarkable in history
- Sleep apnea
- Has noticed feet have enlarged and rings no longer fit

ON EXAM

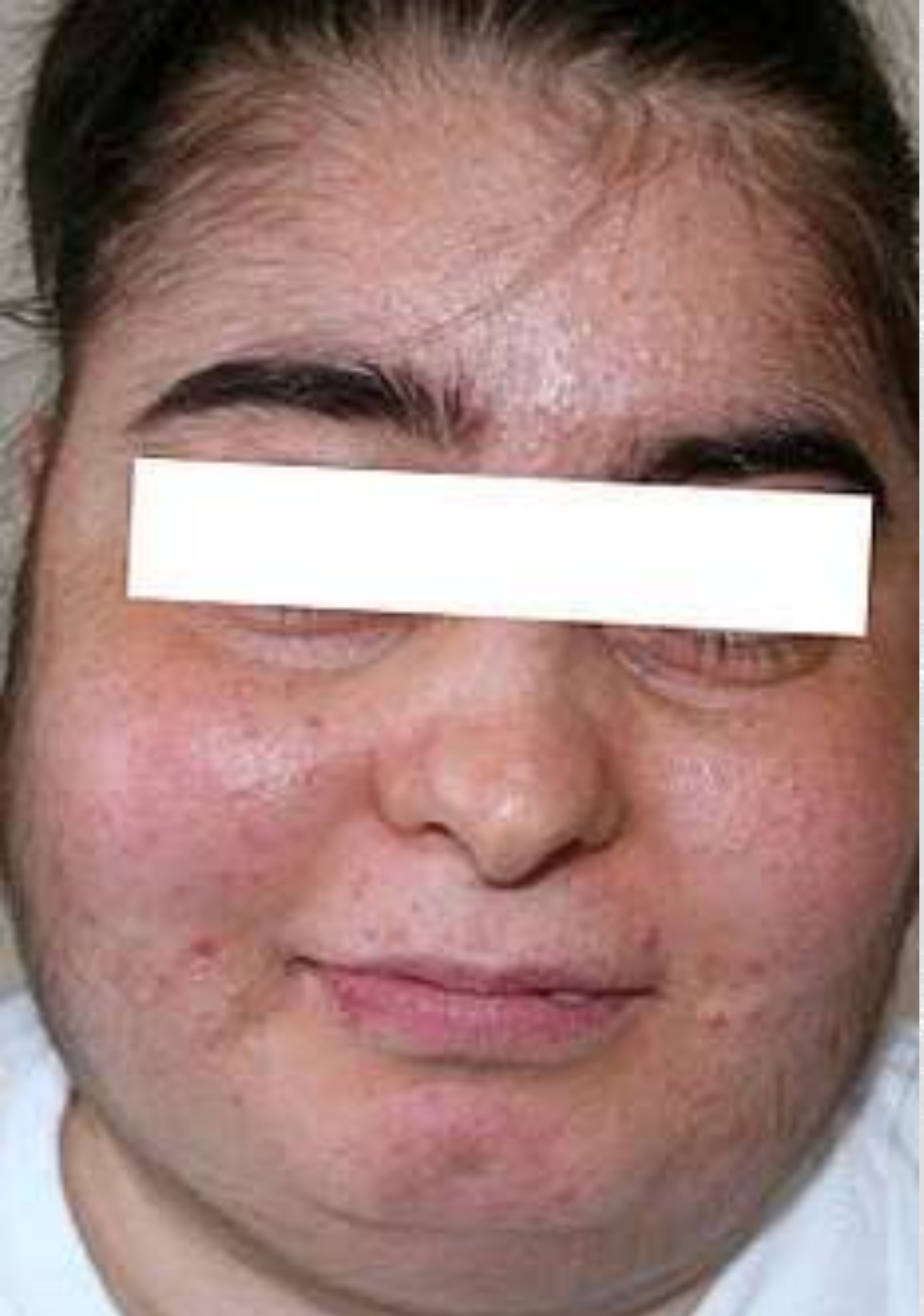
- Bp 140/90
- Macroglossia
- Large hands
- Frontal bossing
- Thyromegaly
- Cvs normal
- Resp clear
- Large thick heels

WAS NOT JUST TYPE 2 DIABETES

- Igf 1 elevated
- Glucose tolerance unsuppressed gh
- Mri small microadenoma
- Transphenoidal in boston;
- Resolved igf1
- A1c now 0.065
- Sleep apnea improved
- TAKE HOME MESSAGE; KEEP YOUR EYES OPEN; VERY SUBLTE CHANGES IF YOU SEE PATIENTS OFTEN MAY NOT NOTICE CHANGES
- HAVE THEM BRING OLD PICTURES

TYPE 2 DIABETES ONLY?

- TYPE 2 DIABETES FOLLOWUP
- WEIGHT GAIN
- NEW STRIAE
- HYPERTENSION
- SO WHAT COMMON IN YOUR PATIENTS
- YOU DON'T WANT TO MISS THIS DIAGNOSIS



CUSHINGS SYNDROME

- DEXAMETHASONE SUPPRESSION
- 100 ; ABNORMAL
- ACTH SUPPRESSED
- MRI ADRENAL NODULE 3 CM
- RESECTED;
- COMPLETE RESOLUTION OF DIABETES
- AND HYPERTENSION

MIDDLE AGED EX ATHLETE

- Family history of dominant
- Lean diabetes
- Early heart disease
- Genes waiting to be discovered
- Come back in 5 years

- Thank you!!!!!!