Atypical and Ketosis-Prone Diabetes

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“Atypical” Diabetes in the Spectrum
“Atypical Diabetes”

- Mendelian / monogenic / oligogenic; syndromic
- Diabetes due to mutations in genes regulating mitochondrial function
- Presenting with islet autoantibodies and features of T2D – insulin-independent at onset
- Presenting with DKA but able to come off insulin therapy, or with fasting serum C-peptide >1 ng/dL
- Requiring insulin from diagnosis, without islet autoantibodies, but with low fasting C-peptide level (<1 ng/dL)
- Criteria for autoimmune T1D with additional autoimmune conditions
- Onset of diabetes without islet autoantibodies at <20 years of age
- Clinical evidence of lipodystrophy
- Poor response to metformin within the first 6 months of treatment, or lack of response to GLP-1 agonist
- Long-term “non-progressor,” i.e., with HbA1c < 7% for >10 years on only metformin
- Forms of “secondary diabetes”
“Ketosis-Prone Diabetes”

Patients presenting with DKA (often as the first manifestation of diabetes), but lacking the phenotype of autoimmune type 1 diabetes
Aβ Classification of KPD

KPD Around the World
Aβ Classification of KPD

Following recovery from DKA, demonstrate sustained preservation of β-cell function with ability to discontinue insulin treatment while maintaining excellent glycemic control.

Case 1

• 17 yo Hispanic woman presented with DKA after stopping insulin Rx for 3 days.
• Dx diabetes 3 y previously; on MDI insulin from diagnosis
• H/o diabetes in mother (dx in her 30’s, on insulin) and maternal grandmother (dx in her 60’s, on no medications)
• Past history of DKA
• BMI 24 kg/m², physical exam unremarkable
• No evidence of infection, CAD, CVD, renal / liver dysfunction, drugs, alcohol
• ABG consistent with DKA, AG 24
• Standard treatment for DKA, uneventful recovery and discharge on insulin
Case 1

WHAT KIND OF DIABETES DOES SHE HAVE?
Case 1 – additional information

- HbA1c = 13.8%
- Islet autoantibodies: Negative for GAD65Ab, IA-2 Ab, ZnT8 Ab
- C-peptide:
  - Fasting: < 0.05 ng/mL
  - Peak after glucagon stimulation: < 0.05 ng/mL
- Current Rx: MDI insulin
- HbA1c on follow-up: range from 7.5% (before pregnancy) to 11.2%
Case 1 - Diagnosis

• Dx: A-β- KPD

• 26% monogenic
• This patient does not have a mutation in any known gene associated with monogenic diabetes
• What of the other 74% ??
Case 2

- 56 y.o. African-American man presented with DKA
- No prior history of diabetes
- Polyuria and 25 lb weight loss in the preceding 2 months
- Past history: Hypertension
- Family history: One brother with diabetes on oral medication
- No smoking, alcohol
- BMI 29 kg/m²
- Mild acanthosis nigricans on neck
- Central obesity, otherwise unremarkable physical exam
- No evidence of infection, CAD, CVD, renal / liver dysfunction, alcohol
- Standard treatment for DKA, uneventful recovery and discharge on insulin
Case 2

WHAT KIND OF DIABETES DOES HE HAVE?
Case 2 – additional information

• HbA1c 12%
• Islet autoantibodies: GAD65Ab positive (high titer), IA-2 Ab and ZnT8 Ab negative
• Central obesity, otherwise unremarkable physical exam
• C-peptide 2 weeks after DKA:
  Fasting: 1.5 ng/mL
  Peak after glucagon stimulation: 1.62 ng/mL
• C-peptide 6 months later:
  Fasting: 2.6 ng/mL
  Peak after glucagon stimulation: 5.2 ng/mL
• Insulin discontinued 6 months after DKA episode
• Current Rx: metformin 2g/d, glimepiride 4 mg/d, pioglitazone 15 mg/d
• Remains off insulin 2 years after DKA, no further DKA, HbA1c levels 6.2% - 7.8%
Case 2 - Diagnosis

• **Dx:** A+β+ KPD

• Have both TID susceptibility and T1D protective HLA Class I alleles
• High frequency of an epitope-specific GAD65 Ab (“DPD”)
• Circulating insulin DNA (unmethylated and methylated)
• Natural history: ~ 50% have declining beta cell function over 1 year and become insulin-requiring; ~50% have stable beta cell function over 3-4 years and remain insulin-independent
Case 3

• 44 y.o. Hispanic man presented with DKA
• No prior diagnosis of diabetes
• Polyuria and 30 lb weight loss over 1 month
• Past history: Nil significant
• Family history: Both parents and a sister with diabetes on oral medication
• No smoking, occasional alcohol
• BMI 36 kg/m²
• Mild acanthosis nigricans on neck
• Central obesity, otherwise unremarkable physical exam
• No evidence of infection, CAD, CVD, renal / liver dysfunction, alcohol
• Standard treatment for DKA, uneventful recovery and discharge on insulin
Case 3

WHAT KIND OF DIABETES DOES HE HAVE?
Case 3 – additional information

- HbA1c 12.4%
- Islet autoantibodies: Negative for GAD65Ab, IA-2 Ab and ZnT8 Ab
- Central obesity, otherwise unremarkable physical exam
- C-peptide 2 weeks after DKA:
  - Fasting: 3.6 ng/mL
  - Peak after glucagon stimulation: 6.6 ng/mL
- C-peptide 6 months later:
  - Fasting: 3.2 ng/mL
- Insulin discontinued 4.5 months after DKA episode
- Current Rx: metformin 1g/d
- Remains off insulin 4 years after DKA, no further DKA, HbA1c levels 5.2% - 6.1%
Case 3 - Diagnosis

• Dx: A-β+ KPD

A-β+ KPD

• “Unprovoked” and “Provoked”
  • Different natural histories and pathophysiology
  • Unprovoked:
    Male predominant
    Low frequency of HLA susceptibility alleles
    Absent T cell reactivity to islet antigens
    Defects in branch chain AA metabolism, arginine metabolism
    Beta cell function stable and insulin-independent for > 4 years (median)
  • Provoked:
    One-third have T cell reactivity to islet antigens
    Progressive decline in beta cell function; require insulin within 2 years (median)