MODY 2 diabetes in Siberia: 3 years of follow

Alla Ovsyannikova, PhD,
Federal State Budget Institution "Scientific Research Institute of Therapy and Preventive Medicine", Russia, Novosibirsk
The population in Russia is 146,519,759 people, in Novosibirsk – 1,584,000
The number of patients with DM in Russia

- **Russia**:
  - DM: 3.0
  - Type 1: 0.05
  - Type 2: 3.0

- **Novosibirsk**: Not shown in the diagram.
Prevalence of DM in youth in Russia*

12% type DM 1
3% nonimmune forms of DM
85% LADA

The prevalence of nonimmune forms of DM in Russia*

- MODY: 36%
- DIDMOND: 17%
- Neonatal DM: 13%
- Rare forms of DM: 12%
- Syndrome of Alstrem: 16%
- Type 2 DM: 4%

n=296

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>MODY</th>
<th>TYPE 2 DIABETES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of inheritance</td>
<td>Monogenic, autosomal dominant</td>
<td>Polygenic + environment</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Childhood, adolescence or young adulthood (&lt;25yr)</td>
<td>Adulthood (40-60yr) occasionally adolescence (obese)</td>
</tr>
<tr>
<td>Pedigree</td>
<td>Usually multigenerational</td>
<td>Rarely multigenerational</td>
</tr>
<tr>
<td>Penetrance</td>
<td>80-95%</td>
<td>Variable (~10-40%)</td>
</tr>
<tr>
<td>Body habitus</td>
<td>Nonobese</td>
<td>Usually obese</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Absent</td>
<td>Usually present</td>
</tr>
</tbody>
</table>

M. Vaxillaire et al., 2006
Definition of MODY

S. Fajans и R. Tattersall entered abbreviation of MODY in 1965 year

↓

first mutation (gene glucokinase) was diagnosed in 1992

↓

five subtypes of MODY were identified in 2002

↓

NOW: 13 subtypes of MODY
Characteristics of MODY diabetes*

- relatives with disorders of carbohydrate metabolism;
- manifestation of DM before the age of 25 years;
- the absence of ketoacidosis;
- good compensation (HbA1c ≤ 7%) diabetes;
- long-term (at least 1 year) remission ("honeymoon diabetes") without periods of decompensation;
- preservation of the secretory activity of beta cells (the level of C-peptide is in the normal range or slightly reduced);
- Absence of markers of autoimmune response against beta cells (antibodies to beta-cells, GAD, insulin);
- Absence of obesity;
- absence of association with HLA.

*M. Vaxillaire et al., 2006, Ch. Henzen, et al., 2012;
Pancreatic β-Cell and the Proteins Implicated in MODY

Glucose sensing

Insulin gene expression

MODY types*

HNF 4a (hepatocyte nuclear factor)
  GCK,
  HNF-1a,
  IPF (insulin promoter factor),
  HNF-1b,
  NEUROD1
  KLF-11,
  CEL,
  PAX-4,
  INS,
  BLK
  ABCC8
  KCNJ11

New types (2012)

• Ch. Henzen, 2012, B. Johansson, 2011, Bowman et al., 2012
Prevalence of subtypes MODY diabetes

- MODY 2-5% of all cases of diabetes, in the UK up to 10%.
- MODY 3:
- MODY 2:
Prevalence of subtypes MODY diabetes in Russia

MODY 2 = MODY 3
Phenotype of MODY 2*

- Symptoms;
- Can begin to
- Good compensation;
- Moderate fasting hyperglycemia (not more than 6.5 mmol/l);
- OGTT: increase in blood glucose of less than 3.5 mmol/l;
- Neuropsychiatric disorders 7.5%;
- Absence obesity.

*A. Senatorova et al., 2009*
Characteristics of carbohydrate metabolism in MODY 2

n=67

- 48% normal glucose
- 38% hyperglycemia
- 14% DM

2 Russian Congress «Innovative technologies in endocrinology» (May 2014)
Treatment of MODY 2

**Children**
- Diet: 86%
- Insulin: 7%
- Drugs: 7%

**Adult**
- Diet: 70%
- Insulin: 3%
- Drugs: 27%

2 Russian Congress «Innovative technologies in endocrinology» (May 2014)
**MODY GCK in Siberia**

- **The purpose:** to identify the clinical features of MODY GCK diabetes which we need to follow of this group of patients.

*The reported study was supported by RSCF, research project No. 14-15-00496.*
• **Materials and methods:**
  - diagnose of MODY GCK during the molecular genetic testing of glucokinase gene;
  - once a year: full clinical examination, blood samples for biochemical research, determination of C-peptide and TSH, antibodies to b-cells, microalbuminuria, abdominal ultrasound, heart and thyroid ultrasound, examination of ophthalmologist.
Results

Patients with MODY GCK:

• 14 peoples (8 probands +6 relatives) = 6 males (43%) and 8 (57%) female.
• The average age of the probands was 12 ± 2,6 years.
• Age of onset ranged from 3 months to 32 years.
• Median of duration of diabetes was 3 years.
• Hereditary: 93% of patients had relatives with disorders of carbohydrate metabolism, 1 patient had mutation “de novo”.
Results

• Mutations were in 1 ekzon, 3, 4, 5, 7 of GCK gene.

• Mutation 60 C > T
Results

DEBUT:

Asymptomatic debut

Patients with MODY 2

Fasting hyperglycemia
Results

DEBUT:

- Thyroid pathology
- Allergic reactions
- Dyslipidemia
- Bronchial asthma
- Arterial hypertension
Results

• Diabetes complications:
  1 patient (7%) had diabetic nephropathy, chronic kidney disease, Stage 1, category 2 (A2).
Results

3 YEARS OF FOLLOW UP:

• Overweight and obesity were not detected in any patient.

• The same patient had no progressive diabetic nephropathy.

• Biochemical analysis: no changes.
Results

HbA1c

- 3 years of follow: 6.2%
- Debut: 6.6%

C-peptide

- 3 years of follow: 0.9 ng/ml
- Debut: 1.1 ng/ml

- 3 years of follow
- Debut
Results

Percentage chart showing the comparison between diet, insulin, and oral drugs over time:
- **Diet**: Approximately 80% for Debut and 50% for 3 years of follow-up.
- **Insulin**: Low percentage for both Debut and 3 years of follow-up.
- **Oral drugs**: Approximately 20% for both Debut and 3 years of follow-up.

Legend:
- **Debut**
- **3 years of follow**

Note: The exact percentages need to be determined from the chart.
Conclusions

1. The earliest age of clinical manifestations of disorders of carbohydrate metabolism in MODY 2 diabetes was six months which should be considered in the differential diagnosis with type 1 diabetes because it is also manifest in a younger age group.

2. MODY 2 diabetes had oligosymptomatic onset, soft flow, good compensation of carbohydrate metabolism, no complications, no need for exogenous insulin in most cases.
Clinical case

- Patient D. (boy) 2002 year of birth.
- 2010 year: thirst, itchy skin. Fasting hyperglycemia 6.5 mmol/l (capillary blood), postprandial hyperglycemia 8.9 mmol/l, HbA1c 5.9 %. Antibodies to b cells, GAD negative.
- The patient had diabetic nephropathy, chronic kidney disease, Stage 1, category 2 (A2).
Clinical case

• Relatives of the patient did not have diagnosis of diabetes.
• 2012 genetic research of GCK gene. Mutation 146 (146C > G) was detected.
• Probands parents were examined. Father had asymptomatic fasting hyperglycemia. He was examined and same mutation was detected.
Pedigree

Hyperglycemia

MODY 2

Hyperglycemia

MODY 2
• **Probands father had mild hypertension.**
Clinical case

• Treatment in 2012:
  - Patient: Insulin (4-6 U Detemir)
  - Father: diet.

• Treatment in 2015:
  - Patient: glibenclamid ¼ tab 1,75mg
  - Father: diet.
Thank you for your attention!