The challenges of diagnosis and treatment of a rare form of MODY1 diabetes

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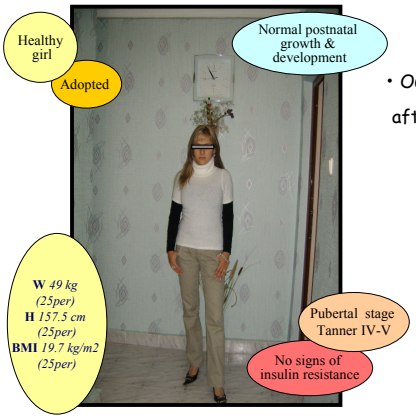
Introduction

- A 16-years old girl with complaints of progressive diabetic symptoms (polyuria, nocturia and polydipsia) for 3 months before the admission
- Weight loss of 6 kg, despite her increased appetite
- No other clinical signs of deterioration
- Normal physical examination
- **FBG levels: 9.0-9.4 mmol/l**
- **HbA1c: 9.1%**
- Referred for further evaluation and treatment



Investigations:

- OGTT with BG increasing from 8.4 to 24.5 mmol/l at 120' after that – BGL 10.0 at fast to postprandial 21.8 mmol/l
- Normal electrolytes and no acidosis,
- Normal hepatic and renal function,
- Normal TSH, elevated Tg and decreased HDL-C
- Urine analysis – glucose (++/++++), ketones (-)

Family history of diabetes ???
What about autoimmunity ???

The initial DD was autoimmune type 1 DM or MODY because of:

- age at presentation <25 years
- lack of obesity and insulin resistance
- progressive hyperglycemia
- no tendency to DKA without insulin treatment

I. Type 1
β-cell destruction, usually leading to absolute insulin deficiency
A. Autoimmune
B. Idiopathic

II. Type 2
may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance

III. Other specific types

A. Genetic defects of β -cell function
1.Chromosome 12, HNF-1α (MODY3)
2.Chromosome 7, glucokinase (MODY2)
3.Chromosome 20, HNF-4 α (MODY1)
4.Chromosome 13, insulin promoter factor- (IPF-1; MODY4)
5.Chromosome 17, HNF-1β (MODY5)
6.Chromosome 2, NeuroD1 (MODY6)
7.Mitochondrial DNA mutation
8.Chromosome 7, KCNJ11 (Kir6.2)
9.Others

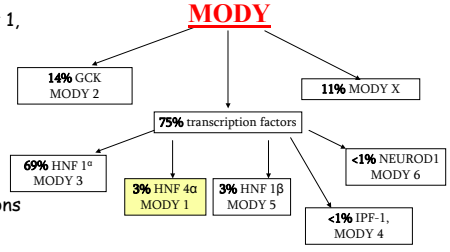
B. Genetic defects in insulin action
1.Type A insulin resistance 2. Leprechaunism 3. Rabson-Mendenhall syndrome 4. Lipoatrophic diabetes.
2.Others. Diseases of the exocrine pancreas.

	MODY	*Type 2*	*Type1*
Non insulin dependent	Yes	Yes	No
Parents affected	1	1-2	0-1
Age of onset < 25yr	Yes	unusual	Yes
Obesity	+/-	+++	+/-
Acanthosis Nigricans	-	++	-
Racial groups (Type 2 prevalence)	low	high	low
Glycaemia	Variable	Variable	Variable
Autoantibodies ICA, IA2 or GAD	Not present	unusual	>95% diagnosis
C-peptide	Usually detectable	not measurable	detectable, may be high

MODY (Maturity Onset Diabetes in the Young)

6 different diseases, with distinct clinical picture, only some of which are insulin-dependent
All these diseases are already discovered single genes mutations

- Start in younger age, usually below 25, in at least 1, ideally 2 or more family members
- Insulin independent, at least in the first 3 years after diagnosis, with measurable C-peptide, the constant part of the insulin molecule.
- No tendency towards DKA
- Strong inheritance trait, in 2, ideally 3 generations
- Lack of obesity or insulin resistance



Treatment:

S.c. insulin therapy (10/06) with rapid- and long-acting insulin analogues 1 IU/kg, controlled by BG monitoring - BG levels immediately dropped to 6.5-12 mmol/l. For further 3 weeks the insulin dose did not decrease, *BGL remained between 7.0 – 13.4 mmol/l (no remission)*
After 3 weeks - confirming lack of autoimmunity GAD-65 0.16 IU/l [<5],IA-2 0.3 IU/l [<0.9], IAA 3.57 IU/l [<10] and C-peptide 1008 pmol/l [170-980]

Glipizide was started up to 2x1 t., ↓ ins. dose in parallel; cessation of Insulin – *on the 10th day* of the oral treatment; 1 month later ➔ HbA1c - *6.9%,* but midday hypoglycemia – 2.0-2.5 mmol/l diet, physical activity and Diaprel MR 1 t./day for another 3 mths. At 6th month HbA_{1c} – *7.4%* due to profound dietary mistakes. Further episodes of improvement and deterioration.

In 2009

A HNF-4α mutation (R244Q) was confirmed by sequencing the gene

What's rare?

> 20 000 000 people in the world on insulin
0.02% ever tested for monogenic diabetes
↳ Galina's testing № is 4260!
189 with genetically proven HNF-4α (MODY1)
0.00094%!
R244Q mutation – only 1 published and 1 other known patient – *0.00001%!*

Galina is pregnant now !!!
Treatment during pregnancy

Individuals with HNF4A diabetes are often sensitive to sulphonylureas and if the patient is already on sulphonylureas and their blood glucose control pre-pregnancy or in early pregnancy is excellent then it may be appropriate to continue this treatment as changing treatment may lead to worsening of diabetes control at a critical time of fetal development.
If the baby inherits the change in the HNF4A gene from their parent then on average they will be 800grams heavier (*babies are often born >5kg or11lbs at term*) and there is therefore the possibility of obstetric complications and prolonged hypoglycaemia of the baby is often seen. This difference in birth weight is seen when the change in the HNF4A gene is inherited from the mother or the father. The increased birth weight is probably due to increased foetal insulin secretion. If the baby is unaffected then the pregnancy will be similar to a typical diabetes pregnancy where excellent blood glucose control is still critical to try to reduce macrosomia.
(DiabetesGenes MODY pregnancy/birth Guidelines)

Conclusion

The prognosis and the prevention of the complications of such forms of diabetes are highly dependent on the timely and true diagnosis, since it defines the therapeutic approach

Pregnancy – still further challenges…

For more information: www.diabetesgenes.org , *Ellard et al., Diabetologia 2008 "Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young"*

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