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

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

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

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. insuline therapy (10/06) with rapid- and long-acting insuline analogues 1 IU/kg, controlled by B6 monitoring - B6 levels immediately dropped to 6.5-12 mmol/l. For further 3 months the insulin dose did not decrease, BGL remained between 7.0 – 13.4 mmol/l (no remission)

Galina is pregnant now !!!

What’s rare?

> 20 000 000 people in the world on insulin
0.02% ever tested for monogenic diabetes
Galina’s testing Ns is 4260!
189 with genetically proven HNF-4a (MODY1)
R244Q mutation – only 1 published and 1 other known patient – 0.00001%

In 2009

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

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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