



Transient hyperglycaemia preceded by neonatal hyperinsulinaemic hypoglycaemia in an infant with a novel *HNF1A* mutation

Obermannova Barbora, Rozenkova Klara, Dusatkova Petra, Sumnik Zdenek, Pruhova Stepanka, Lebl Jan
Department of Paediatrics, 2nd Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic

The authors have nothing to disclose



INTRODUCTION

Hepatocyte nuclear factor HNF-1 α is known to cause maturity-onset diabetes of the young (MODY), which is characterized by autosomal-dominant inheritance and impaired glucose-stimulated insulin secretion from pancreatic beta-cells.

The phenotype associated with heterozygous *HNF1A* gene mutations has recently been extended to include neonatal hyperinsulinaemic hypoglycaemia (HH) connected with macrosomia (Fig. 1.) in addition to maturity-onset diabetes of the young (HNF1A-MODY). These mutations are usually connected with HH family history consistent with MODY.

CASE PRESENTATION

The baby boy was born at 38 weeks of gestation; BW 4110 g; BL 53 cm (LGA). The boy developed hypoglycaemia since the first day of life that required intravenous glucose administration; during hypoglycaemia (2.0 mmol/L) the level of insulin was not suppressed (4.2 mIU/L) confirming HH. After the neonatal period, hypoglycaemias resolved spontaneously. At the age of 10 months, the boy developed acute respiratory failure during viral pneumonia with severe dyspnoea, tachypnoea and dehydration. At admission, he had hyperglycaemia 18 mmol/L (before any treatment) and mild acidosis (pH 7.2, HCO₃ 20 mmol/mol); he had no history of polyuria and polydipsia. His HbA_{1c} was 34 mmol/mol, he had low C-peptide (334 pmol/L); diabetes associated antibodies (a-GAD, a-IA2, a-IAA) were negative. During the subsequent therapy with high-dose corticosteroids and mechanical ventilation, he required continuous insulin infusion (0.01 IU/kg/h) for seven days. Insulin therapy could be discontinued after the respiratory stabilization, afterwards the glycaemia remained normal. Today, at the age of 17 months the boy is without any treatment and his actual HbA_{1c} is in lower normal range (29 mmol/mol).

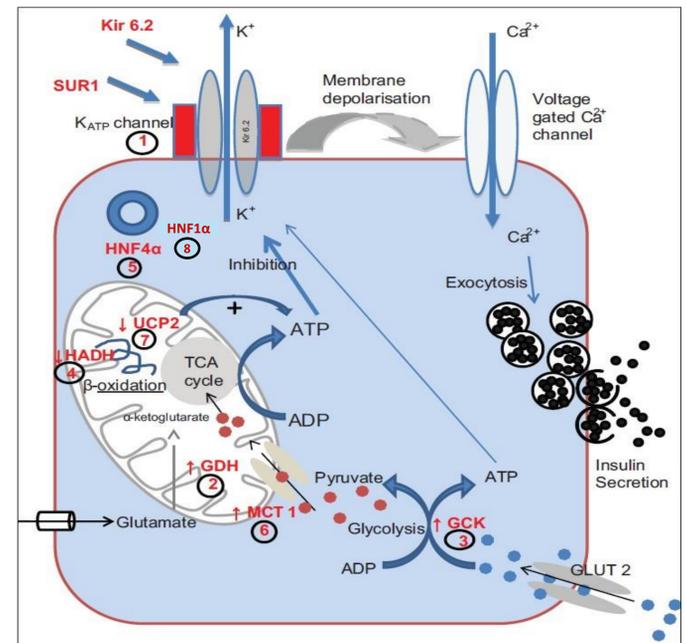


Figure 1.: Aetiology of Congenital Hyperinsulinism: the known genes (1-7) were recently extended to the Hepatocyte Nuclear Factor 1 α (8).
According to Senniappan, *Indian J. of Endocrinology and Metabolism*, 2013

FAMILY HISTORY

There is family history of LGA, HH and diabetes (Fig. 2.): mother of the child was born LGA, she had gestational diabetes in both pregnancies and her actual HbA_{1c} is 39 mmol/mol. Her father is treated with sulfonylurea for diabetes mellitus since 18 years of age. Her brother was born LGA, his HbA_{1c} is 36 mmol/mol. The older sister of the proband was born LGA, she had transient HH in newborn period, her HbA_{1c} is 35 mmol/mol.

GENETIC TESTING

Methods

Because of the positive family history of HH and diabetes in proband and other family members we performed molecular genetic testing of *HNF4A* and *HNF1A* gene using direct sequencing.

Results

The proband, his mother, his sister, maternal grandfather and uncle were shown to carry a **novel** heterozygous mutation (L254Q) in the *HNF1A* gene (Pedigree Fig 2.).

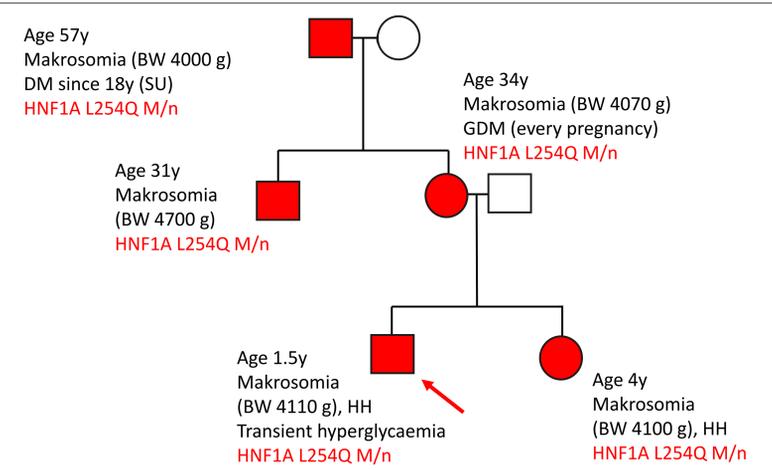


Figure 2.: Pedigree of affected family: family history of macrosomia, HH and diabetes

DISCUSSION

The fetal macrosomia and neonatal hyperinsulinaemic hypoglycaemia in childhood is not limited only to *HNF4A* mutations, but is connected also to *HNF1A* mutation. It may be due a biphasic impact of the *HNF1A* mutation on beta-cell function over the lifespan, leading from insufficient control of insulin oversecretion to final failure of insulin production.

The failure of the insulin secretion manifest as MODY can onset at every age (common is adolescence or young adulthood) and usually continues over the whole life.

During the stress period in our patient occurred transient hyperglycaemia requiring insulin treatment with subsequent complete recovery.

CONCLUSION

To our knowledge, this is the first observation of HNF1A-MODY with a history of neonatal hypoglycaemia followed by transient stress hyperglycaemia in infancy.

This suggests that the capacity of beta-cells to respond to high demands on insulin secretion may be impaired since an early age.