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LETTER TO THE EDITOR

Macrosomia, transient neonatal hypoglycemia, and monogenic diabetes in a family with heterozygous mutation R154X of HNF4A gene

Congenital hyperinsulinemic hypoglycemia (CHI) is a potentially life-threatening condition which is often caused by loss-of-function mutations in *ABCC8* and *KCNJ11* genes, that encode for the ATP-sensitive potassium channel of the pancreatic β cell. Recently, it has been shown that in families with monogenic diabetes due to genetic defects of the transcription factor HNF4A [known as Maturity Onset Diabetes of the Young type 1 (MODY1)] mutation carriers can present neonatal hypoglycemia and macrosomia (1).

Here we report about a girl born large for gestational age, who showed severe neonatal hypoglycemia (day 1 of life) treated with glucose infusion (Table 1). She had a second hypoglycemic episode at day 9, treated again with glucose infusion for 2 days. Her younger sister, who was delivered by cesarean section because of macrosomia and polyhydramnios at 34 weeks of gestation, also presented with mild, transient neonatal hypoglycemia. Both were referred to us for molecular genetic screening. Family history disclosed early-onset Type 2 diabetes in the mother and in the maternal grandfather. In particular, the mother had been diagnosed with gestational diabetes – treated with insulin – during her second pregnancy (35 yr of age) and, after a year free of therapy, started on oral hypoglycemic agents. These data combined prompted us to screen directly the *HNF4A* gene in this family. We identified a C>T substitution at position 460 (c.460C>T), resulting in the already described mutation arginine→stop at codon 154 (p.R154X) (Table 1) in the proband, her sister, and her mother. DNA of maternal grandfather, deceased, was not available. The proband, now almost 15 yr old (pubertal stage: Ph5,B5), and a bit overweight, has shown at the last visit above normal glycated hemoglobin value compatible with recently proposed criteria for diagnosis of diabetes (2). This finding is in line with what is usually seen in patients with heterozygous mutations of *HNF4A* gene or *TCF1*/HNF1A (so-called MODY 3), who present with diabetes at adolescence or as young adults.

Mutations of HNF4A have been associated to both transient (1, 3, 4) or persistent, diazoxide-responsive form of CHI (1, 5, 6), with no apparent correlation between mutation type and clinical outcome of hypoglycemia (i.e. transient *vs* persistent) (1). Mutation HNF4A/R154X has already been described in patients with MODY 1 (7); this is the first time, however, that it has been associated with macrosomia and neonatal hypoglycemia. It has to be taken into account, however, that prematurity *per se* is also considered a risk factor for neonatal hypoglycemia and that the low plasma glucose found in a single occasion in proband's sister, born at the 34th week of gestation, may also be due to this fact. Dominant heterozygous mutations of *ABCC8* and *KCNJ11* genes causing CHI may also be rarely associated with Type 2 diabetes in adult family members carrying the genetic defect (8). Thus, families with the aforementioned clinical features may be challenging in terms of molecular genetic diagnosis. In summary, we confirm that the presence of macrosomia and neonatal hypoglycemia in a family with history of diabetes is a strong indicator of a mutation in the *HNF4A* gene and suggest that in cases analogous to the one reported here, molecular genetic screening of this gene should be performed as first step.

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Table 1 - *Clinical features of family members carrying the HNF4A/R154X mutation.*

	Proband	Sister	Mother
Mutation HNF4A/R154X	n/m	n/m	n/m
Birth weight (g), weeks of gestation, percentile	4220, 40, >>97°	2620, 34, 90°	n.a.
Plasma glucose at birth (mg/dl)	17 (day 1 of life) 33 (day 9 of life)	31 (day 1 of life)	n.a.
Current age	14 yr, 10 m	10 yr, 6 m	45
Current BMI	28.8	20	25.9
Current HbA_{1c} % (mmol)	7.3 (56)	5.3 (34)	8.2 (66)
Current therapy	None	None	Glargine 8 U/d + OHA

n/m: normal/mutant; BMI: body mass index; OHA: oral hypoglycemic agents; HbA_{1c}: glycated hemoglobin.

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