Hyperinsulinemic hypoglycemia without insulinoma: Think of activating glucokinase mutation

Congenital hyperinsulinism (CHI) is a rare condition that can lead to persistent severe hypoglycaemia, mostly discovered in neonates and infants, exceptionally in adulthood [1,2]. The present report describes a case of CHI discovered in adult, mimicking insulinoma but without radiological abnormalities, leading to the identification of a novel Glucokinase (GCK) activating mutation.

A 25-year-old woman without significant medical history was referred for unexplained severe hypoglycaemia. At the bedside, hypoglycaemia was confirmed with a blood glucose measurement of 45 mg/dL and HbA1c of 4.2% (n < 6.5). She had noticed fluctuating episodes of mid-morning tiredness, hunger, headaches relieved by food, and night sweats since childhood. These symptoms occurred both during fasting and after eating. She was not taking any medication. The physical examination was normal. Her BMI was 26.2 kg/m² and stable. An oral glucose tolerance test (OGTT) revealed hyperinsulinemia (120 min post-stimulation: glucose 37 mg/dL, insulin 3.2 mIU/L [normal: 2.5-10.4], C-peptide 6.19 ng/mL [normal: 0.95-2.30]). A fasting test (table SI) induced an episode of unexplained hypoglycaemia after 32 h. Of note was that the glucose level remained between 43 and 57 mg/dL without any complaint, and no lower values. Biological investigations eliminated iatrogenic, metabolic, adrenal or pituitary causes of hypoglycaemia. Abdominal CT scan, pancreatic MRI, endoscopic ultrasound, octreoscan scintigraphy and fluorine-18-6-fluoro-L-dopa PET scan, revealed no insulinoma. Continuous glucose monitoring (CGM) (figure 1A) showed a low mean glucose, especially during the night, reproducible day-to-day, but with no severe hypoglycaemia.

A CHI Next-Generation-Sequencing (NGS) analysis revealed a heterozygous mutation (c.538A > G; p.Asn180Asp) of the GCK gene, never reported in literature. Bioinformatics prediction systems (SIFT, Polyphen) argued for a pathogenicity of this variant. The patient's mother and sister presented also hypoglycaemia symptoms. The mother refused all medical examination. The mutation was therefore identified in the 30-year-old sister, BMI of 25 kg/m², who complained of tiredness and uneasiness, relieved during her single pregnancy and by food. Her random blood glucose was 56 mg/dL with a concomitant insulin level of 5.8 mIU/L and a HbA1c of 3.9%. A fasting symptomatic hypoglycaemia occurred during hospitalization with a blood glucose and insulin levels respectively of 47 mg/dL and 3.2 mIU/L. A 4-hour OGTT (table SI) revealed also hyperinsulinaemic hypoglycaemias 90 and 180 min post-stimulation.

Because of permanent low blood glucose level, the proband and her sister had brain MRI and cognitive assessment which were both normal.

The treatment with diazoxide was refused by the proband but accepted by her sister, whose symptoms improved more overtly clinically than biologically with only partial correction of hypoglycaemia (figure 1B, C).

The diagnosis of CHI should be suspected in any adult with hyperinsulinemic hypoglycaemia without image of insulinoma. CHI is defined as a genetic disorder related to at least 11 genes involved in insulin secretion by pancreatic β cells, leading to monogenic hyperinsulinemic hypoglycaemia: ABCG8, KCNJ11, GLUD1, GCK, HADH1, UCP2, MCT1, HNF4A, HNF1A, HK1, PGM1 [1]. Heterozygous activating GCK mutations induce type 2 maturity-onset diabetes of the young (MODY 2). Heterozygous activating GCK mutations induce CHI, accounting for 7% of CHI². In pancreatic β cells, GCK acts as a glucose sensor contributing to maintain glucose homeostasis through glucose-stimulated insulin secretion [3]. In addition to these monogenic forms, there are several syndromic forms of CHI such as Beckwith-Wiedemann, and Kabuki or Turner syndromes [1].

CHI prevalence in adults has not been described yet because of underdiagnosed cases. The diagnosis of CHI may be suggested by a hyperinsulinemic hypoglycaemia, with low or no fatty acids and ketone bodies. A suggestive feature of GCK-CHI is the stability of hypoglycaemia during fasting in our cases like in the description of Challis [4], by contrast with insulinoma, which induces a slowly decreasing blood glucose level. The CGM profile is also of special interest, demonstrating moderate permanent hypoglycaemia without severe hypoglycaemia in our GCK mutation (figure 1A). In contrast, the GCM of an insulinoma shows low blood glucose only during night fast (figure 1D), whereas the CGM profile of a patient affected by a MODY 2 diabetes (inactivating GCK mutation) shows a permanent mildly high mean blood glucose (figure 1E).
Once hypoglycemic hyperinsulinism is confirmed, it is important to define a diagnosis strategy concerning morphological investigations, to avoid costly, invasive, or irradiating morphological investigation, all the more so that new imaging modalities are emerging. When a first CT or MRI exam is negative, we propose the measurement of fasting blood glucose in the kindred which is probably a better strategy than simple questioning about family history. Indeed, in our case report, the symptoms of hypoglycemia in the family were not perceived as possibly abnormal and were not reported until the identification of the mutation. Furthermore, the patients showed curiously no weight gain or neurological repercussions despite recurrent hypoglycaemia. Family hypoglycemia indicates a NGS study to diagnose these rare and perhaps underdiagnosed cases. Fourteen activating mutations of GCK gene always transmitted on an autosomal dominant pattern are known [5]. Penetrance and expressivity are variable ranging from asymptomatic to marked hypoglycemia even for the same mutation in the same family.
This never-reported c.538A > G GCK mutation segregated with the symptoms which were mild and similar in the 2 sisters. They were predicted as pathogenic by the bioinformatic systems and appear as probably activating despite no functional studies were performed.

Treatment of CHI requires first nutritional and medical treatment especially diazoxide administration, an agonist of the SUR1 subunit of the KATP channel. Nevertheless, response to diazoxide varies with genetic mutations and is usually not effective in activating GCK mutation [1,2]. Somatostatin analogues, glucagon or pancreatectomy may be effective in diazoxide-unresponsive CHI [1]. In this study, the proband's sister clinically improved on the long-term with small doses of diazoxide. The development of GCK inhibitors could allow specific treatment for these rare diseases.

Although rarely discovered in adults, monogenic CHI like those induced by activating GCK mutations should be suspected in cases of hyperinsulinaemic hypoglycemia with mild permanent hypoglycemia on CGM, and random low blood glucose in the kindred. This diagnosis is essential to improve the prognosis of CHI’s patients, limit unnecessary radiological investigations and provide family counselling.

Disclosure of interest: AJ and MCV wrote the paper, SE and CD collected data and searched the literature, FP performed the cognitive analysis, CBC performed the NGS study. The authors declare that they have no competing interest.

References


Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.lpm.2018.02.015.