Activating AKT2 Mutation: Hypoinsulinemic Hypoketotic Hypoglycemia

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Background: Hyperinsulinemic hypoglycemia (HH), characterized by unregulated insulin secretion, is an important cause of persistent and severe hypoglycemia (1). The biochemical picture of HH is hypoketotic hypo–fatty-acidemic hypoglycemia along with elevated serum insulin (2). Not infrequently, serum insulin might be undetectable in HH despite the presence of evidence of insulin action (suppressed ketogenesis and lipolysis). However, autonomous activity of the downstream insulin signaling pathway without the presence of the ligand (insulin) will give rise to the same clinical and biochemical picture, apart from undetectable serum insulin/C-peptide. AKT2, a serine/threonine protein kinase, is involved downstream to the insulin receptor in mediating the physiological effects of insulin.

Aim: We describe the second report of an activating AKT2 mutation leading to hypoinsulinemic hypoketotic hypoglycemia.

Patients and Methods: The proband presented with hemihypertrophy and symptomatic hypoglycemia. Investigations confirmed evidence of insulin action, despite absence of detectable serum insulin on multiple occasions. Molecular genetic testing for common causes of HH (ABCC8, KCNJ11, and GLUD1) was negative. Sequencing of AKT2 identified a de novo mosaic c.49G→A (p.E17K) mutation, consistent with the clinical and biochemical phenotype.

Conclusions: This is the second report of an activating AKT2 mutation leading to hypoinsulinemic hypoketotic hypo–fatty-acidemic hypoglycemia. In patients presenting a clinical and biochemical picture of HH with undetectable serum insulin, consideration of autonomous activation of the downstream insulin signaling pathway should be made. (J Clin Endocrinol Metab 99: 391–394, 2014)

Hyperinsulinemic hypoglycemia (HH), characterized by unregulated insulin secretion, is an important cause of persistent and severe hypoglycemia (1). The biochemical picture of HH is hypoketotic hypo–fatty-acidemic hypoglycemia along with elevated serum insulin (2). Not infrequently, serum insulin might be undetectable due to its short half-life in HH (3–5). However, autonomous activity of the downstream insulin signaling pathway without the presence of the ligand (insulin) will give rise to the same clinical and biochemical picture, apart from undetectable serum insulin/C-peptide.

Insulin regulates blood glucose by increasing glucose uptake in peripheral tissues (myocytes and adipocytes) by inducing the redistribution of the glucose transporter 4...
(GLUT4) from intracellular sites to the plasma membrane and by reducing hepatic gluconeogenesis (6, 7). AKT2, a serine/threonine kinase highly expressed in insulin-sensitive tissues, is required for the insulin-induced translocation of GLUT4 to the plasma membrane (8, 9). A missense p.R274H loss-of-function mutation in AKT2 resulted in severe insulin resistance, marked hyperinsulinemia, and diabetes mellitus (10). The opposite phenotype (hypoinsulinemic hypoglycemia) would be expected of a gain-of-function mutation and was recently described in 3 patients (11). We describe here the second report of an activating AKT2 mutation, highlighting the importance for screening for this condition given the characteristic phenotype because management of this condition is very different.

**Case Report**

The proband was born to nonconsanguineous Caucasian parents, at 41 weeks gestation with birth weight and length of 3910 g (+0.78 SD score) and 54 cm (+2.04 SD score), respectively. In the first few months, she had 2 episodes of reduced consciousness that responded well to feeding. No medical opinion was sought. Increasing head size (macrocephaly) and left hemihypertrophy (Figure 1) led to a referral to a specialist at 5 months of age. An ultrasound of the cranium was performed, which was normal.

At 8 months of age, another episode of reduced consciousness resulted in investigations that revealed hypoketotic hypo–fatty-acidemic hypoglycemia with undetectable serum insulin on a controlled diagnostic fast with a fasting tolerance of 3 hours (blood glucose 2.4 mmol/L, serum insulin <2 mU/L, and nonesterified fatty acids and β-hydroxybutyrate ≤0.05 mmol/L). These clinical and biochemical observations suggested the presence of fasting hypoglycemia. Blood glucose improved from 2.4 to 7.3 mmol/L with im glucagon (0.5 mg), providing additional evidence of insulin action despite no detectable serum insulin. The rest of the hypoglycemic screen, including serum cortisol, IGF-1, IGF binding protein 3, serum ammonia, lactate, plasma amino acids, and urine organic acids, was within the normal reference range. A magnetic resonance imaging scan of the brain, including hypothalamus and pituitary, was unremarkable.

Molecular genetic testing for congenital HH and Beckwith-Wiedemann syndrome was undertaken (see below). She was managed with regular feeds during the day and night with the addition of 5 g of corn starch in the night feed. No treatment with diazoxide or octreotide was required. Self-monitoring of blood glucose revealed age-inappropriate fasting tolerance (6 hours at age 4.32 years). After the first description of activating AKT2 mutation, AKT2 sequencing was performed at the age of 4 years in view of a similar phenotype (see below).

With the above management, she has achieved age-appropriate milestones. The latest anthropometry shows weight and height to be at the 91st and 98th centiles, respectively (Figure 2). The left/right mid–upper arm circumference, midforearm circumference, and midthigh circumference was 19/17, 16/15, and 32/31 cm, respectively.

**Genetic analysis**

Genetic testing for Beckwith-Wiedemann syndrome was negative. Sequencing of ABCC8, KCNJ11, and GLUD1 did not identify any mutation. Sequencing of AKT2 identified a mosaic p.E17K (c.49G→A mutation according to NM_001626.3 reference sequence), which was not seen in the parents.

**Discussion**

Mutation in the K_ATP channel genes (ABCC8 and KCNJ11) are the most common causes of congenital HH (12, 13). The other genes implicated in congenital HH include GLUD1, HADH, HNF4A, HNF1A, GCK, SLC16A1, and UCP2 (14–18). The characteristic metabolic footprint of HH is hypoketotic hypo–fatty-acidemic hypoglycemia with detectable serum insulin and C-peptide (2). In our patient, serum insulin was undetectable on 3 separate occasions during hypoglycemia despite conclu-
sive evidence of insulin action. Because serum insulin has a short half-life, it is not uncommon to find undetectable serum insulin in patients with HH. In view of that, we performed sequencing of ABCC8, KCNJ11, and GLUD1 that was negative. We did not perform sequencing for GCK, HNF4A, HNF1A, or SLC16A1 because the clinical picture was not consistent with mutations in these genes (16, 19).

Another unusual finding was the left hemihypertrophy, which, in association with hypoketotic hypoglycemia, led us to consider a recently described activating AKT2 mutation in our patient. In the previous report, 3 patients were described with hypoinsulinemic hypoketotic hypoglycemia and hemihypertrophy due to an activating heterozygous or mosaic c.49G→A (p.E17K) AKT2 mutation (11). AKT2, a serine/threonine protein kinase, is a key mediator of many of the physiological effects of insulin, including the uptake and storage of glucose into insulin-sensitive tissues and inhibition of hepatic gluconeogenesis (20–25). Mutant AKT2E17K exhibited non-insulin-dependent translocation of GLUT4 to the plasma membrane and also prevented hepatic gluconeogenesis, resulting in a biochemical picture of hyperinsulinism despite undetectable serum insulin (11).

Apart from a relatively milder phenotype, our patient had similar clinical and biochemical phenotype and had the identical mutation in the AKT2 gene. As present in our patient, one patient described in the previous report showed 20% mosaicism in lymphocyte DNA. Low-level mosaicism in insulin-responsive tissues might be responsible for the milder phenotype in our patient. In view of the similar phenotype and presence of identical mutation as reported previously, functional work was not considered. Therefore, there are now 4 patients known with the c.49G→A (p.E17K) mutation in the AKT2 gene, suggesting a critical role of glutamine at this position for AKT2 function. Moreover, because all 4 reported patients had hemihypertrophy, we speculate that the mutational change will be present in mosaic form in different body tissues, even in the absence of mosaicism in lymphocyte
DNA. Another evidence of excess insulin action is the pro-band’s height and weight centiles on the growth chart. However, the overgrowth in our patient seems to be predominantly prenatal rather than postnatal. In our experience, these patients are unresponsive to diazoxide and octreotide and maintain euglycemia only with regular carbohydrate feeds.

In conclusion, this is the second report of an activating AKT2 mutation leading to hypoinsulinemic hypoketotic hypo–fatty-acidemic hypoglycemia. Through this case report, we highlight that mutations in AKT2 are a very well-defined clinical phenotype. In patients presenting with HH with undetectable serum insulin, consideration of autonomous activation of the downstream insulin signaling pathway should be made.

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References