Novel syndromes of hypoinsulinaemic, hypoketotic hypoglycaemia

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Introduction
Hypoglycaemia in infancy is commonly caused by hypoinsulinism and is characterised by low ketones, low free fatty acids and low branched chain amino acids during hypoglycaemia, and a high glucose infusion rate to maintain euglycaemia.

Hypoketotic hypoglycaemia in the absence of detectable serum insulin can be caused by an activating mutation in serine-threonine kinase AKT2 (PKBβ) leading to hyperactivation of the AKT2-dependent arm of the insulin signalling cascade (3, 28). These patients have a lower requirement for glucose and show low sided hemi-hypothyrosis.

Here we present a series of five further patients with hypoketotic hypoglycaemia and suppressed insulin but no activating mutation in AKT2, and outline our approach to identifying the underlying genetic and cellular causes.

Patient Group

Patient 1 case history

- born at 35 weeks of gestation. Birth weight 3.05kg (+0.98SD), length 48cm (+0.05SD), and head circumference 35cm (+1.08SD)
- non-consanguineous German parents
- bilateral renal masses noted during gestation (diagnosed as bilateral cystic nephrophy)

Hypoglycaemia (0.4mmol/l) noted at 2 days (Table 1)

- no urinary ketones during hypoglycaemia
- preserved mobilisable glucagon stores as evidenced by glucagon response
- short synacthen test confirmed normal adrenal function; steroid insensitivity
- required parenteral glucose (10-19mg/kg/day) to maintain euglycaemia

Left adrenal mass noted post-natally on ultrasound

- surgical removal did not improve hypoglycaemia
- histology revealed a high-grade adenoma, tumour with normal parenchyma

Left sided hemi-hypothyrosis noted at age 2 and an MRI confirmed overgrowth of left-sided abdominal organs.

At 14 years old she had a fasting tolerance of around 5 hours and did not show any signs of developmental delay. Euglycaemia is currently maintained through frequent meals.

Further patients

In addition to patient 1, four further patients have been identified with hypoketotic, hypoinsulinaemic hypoglycaemia. These show a variety of additional features. (Table 2)

<table>
<thead>
<tr>
<th>ID</th>
<th>Fasting glucose (mmol/l)</th>
<th>Insulin (μIU/ml)</th>
<th>Glucagon (ng/ml)</th>
<th>Cortisol (μIU/ml)</th>
<th>ACTH (ng/ml)</th>
<th>Lactate (mmol/l)</th>
<th>pH</th>
<th>HCO₃⁻ mmol/Eq/L</th>
<th>Ketones, organic acidaemia</th>
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<tbody>
<tr>
<td>P1</td>
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<td>Undetectable</td>
<td>&lt;10</td>
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<td>0.37</td>
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<tr>
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<td>&lt;10</td>
<td>139-476</td>
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<td>0.00</td>
<td>0.00</td>
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Acknowledgments and references

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References:

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Conclusions

We present a group of five patients with a novel syndrome of hypoinsulinaemic, hypoketotic hypoglycaemia in the absence of a mutation in AKT2. The patients represent a biochemical phenocopy of the previously reported AKT2 p.Glu17Lys patients but lack basal hyperphosphorylation of AKT2 and downstream kinases. Furthermore, the patients presented have a varied group of additional clinical feature including asymmetric overgrowth, adrenal tumors, polycystic kidneys, hepatic fibrosis, muscle hypotonia and hepatic fibrosis. Further investigations are underway to determine the genetic causes and cellular mechanisms.