Syndromic hypoketotic, hypoinsulinaemic hypoglycaemia due to a mosaic activating phosphatidylinositol 3-kinase (PI3K) mutation

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Introduction

In contrast to hypoglycaemia due to congenital hyperinsulinism, there are patients with a similar metabolic profile of hypoketotic hypoglycaemia, but low insulin levels and relatively low glucose requirements to maintain euglycaemia. So far, four patients with activating mutations in the insulin signal-transducing kinase AKT2 have been described, each also showing a syndromic phenotype including hemihypertrophy (1). We present a 3.5 year-old girl with similar metabolic and syndromic features, but no AKT2 mutation, suggesting a possible mutation in another gene of the same pathway.

Case report

• Non-consanguineous German parents, birth weight 3230g (+2.03 SDS), length 52cm (+1.51 SDS), HC 37.5cm (+2.33DS)
• Recurrent hypoketotic, hypoinsulinaemic hypoglycaemia, unresponsive to diazoxide and somatostatin analogues, currently stable under starch-enriched meals and overnight PEG feeds.
• Other syndromic aspects: Large diastasis recti, syndactyly, short limbs and “chubby” appearance, ventriculo-peritoneal shunt due to Arnold-Chiari Malformation, epilepsy, generalised muscle hypotonia, hyperaemia of the face, dorsal haemangiomata, fibrocystic hepatitis on liver biopsy

Genetics

Exome sequencing undertaken in the proband and parents detected a mosaic mutation (p.Glu726Lys) in PIK3CA, encoding the p110α catalytic subunit of phosphatidylinositol 3-kinase (PI3K), in lymphocyte, hair bulb, fibroblast, cheek swab, and liver DNA from the patient but neither parent:

<table>
<thead>
<tr>
<th>Sample</th>
<th>Mutation burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Father</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>33-36%</td>
</tr>
<tr>
<td>Liver</td>
<td>42-44%</td>
</tr>
<tr>
<td>Blood</td>
<td>22-20%</td>
</tr>
<tr>
<td>Cheek swab right</td>
<td>20-23%</td>
</tr>
<tr>
<td>Cheek swab left</td>
<td>24-26%</td>
</tr>
<tr>
<td>Hair bulb</td>
<td>27-28%</td>
</tr>
</tbody>
</table>

Cellular Studies

Primary dermal fibroblasts of the patient (P3) show a small but significant increase in phosphorylation of downstream AKT at Thr 308/399 and Ser 473/474, lying downstream of PI3K. This hyperphosphorylation level lies in between those observed in AKT2 mutation (1) and PIK3CA p.His1047Leu-associated segmental overgrowth (2).

Discussion

Activating PIK3CA mutations are known to cause a spectrum of segmental overgrowth disorders including Megalencephaly-Capillary malformation (MCAP) syndrome (3), of which our patient shows several typical aspects. The phenotypic spectrum is substantially influenced by the mosaic pattern, e.g. the mutation burden in a respective tissue. So far, hypoglycaemia has not been described in MCAP syndrome.

Conclusions

In contrast to hypoglycaemia due to congenital hyperinsulinism, there are patients with a similar metabolic profile of hypoketotic hypoglycaemia, but low insulin levels and relatively low glucose requirements to maintain euglycaemia based on mutations in the PI3K/AKT signalling pathway. These patients provide a unique opportunity to study this pathway in vivo.

Acknowledgements and literature

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References:

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