Two patients with HADH (SCHAD) Hyperinsulinism in part without detectable 3-Hydroxybutyrylcarnitine/ 3-Hydroxyglutarate

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Introduction

Congenital hyperinsulinism of infancy (CHI) is the most common cause for persisting hypoglycaemia in infancy. The most common genetic causes are mutations in ABCC8 or KCNJ11 (coding for K⁺-ATP-channel subunits), less frequently mutations in GCK or GLUD1. Further genetic analysis is often performed only if phenotypic aspects point to other specific genes, such as the very rare short chain 3-Hydroxyacyl-CoA dehydrogenase (HADH/SCHAD) deficiency. This disorder is usually characterized by an accumulation of 3-hydroxybutyrylcarnitine in plasma and 3-hydroxyglutarate in the urine.

Methods

Patient 1: No mutations in ABCC8, KCNJ11. Therefore extensive next-generation sequencing (NGS) was performed.
Patient 2: Sanger-sequencing of ABCC8/KCNJ11, GLUD1, GCK did not lead to a conclusive genetic diagnosis, and was followed by further Sanger sequencing of HADH and HNF4A.

Biochemical analysis: Acylcarnitine-profile (blood) and organic acids (urine) via tandem mass spectrometry in patient 1.

Results

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Gene</th>
<th>Mutation</th>
<th>Biochemical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 J</td>
<td>m</td>
<td>HADH</td>
<td>HOM c.428T&gt;A (p.Ile143Asn), new mutation</td>
<td>no detection of significant concentrations of 3-OH-Butyrylcarnitine or 3-OH-Glutarate.</td>
</tr>
<tr>
<td>9 J</td>
<td>w</td>
<td>HADH</td>
<td>HOM c.706C&gt;T (p.Arg236*), mutation published before¹</td>
<td>no analysis.</td>
</tr>
</tbody>
</table>

Conclusions

HADH deficiency should be considered in patients with CHI who are negative for ABCC8 and KCNJ11, and might be more frequent than known so far. Its specific biochemical markers are not necessarily present in individual patients or situations, and should not be regarded as a prerequisite for sequencing of HADH gene.

These data underline the broad clinical and genetic heterogeneity of CHI, and the value of extensive sequencing, e.g. using NGS, to detect the molecular cause of the disease.

Acknowledgements and literature

Written and informed consent was obtained from parents before inclusion in the study.

Literature:
4. OMIM Database: http://www.omim.org/entry/601609, retrieved 26.08.2018

Patients: clinical presentation

Two patients of turkish origin, consanguineous parents. 
Patient 1: male, 17 years, postnatal macrosomy, recurrent hyperinsulininaemic hypoglycaemia since birth, diazoxide responsive (still ongoing, 4,5 mg/kg/d, side effect: hypertrichosis), mild cognitive impairment, obesity, older sister and grandmother also suffering from CHI.

Patient 2: female, 9 years, recurrent hyperinsulininaemic hypoglycaemia since birth, diazoxide responsive (still ongoing, 5mg/kg/d), PET-CT: diffuse form of CHI, normal cognitive function, grandfather and cousin also suffering from CHI.

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