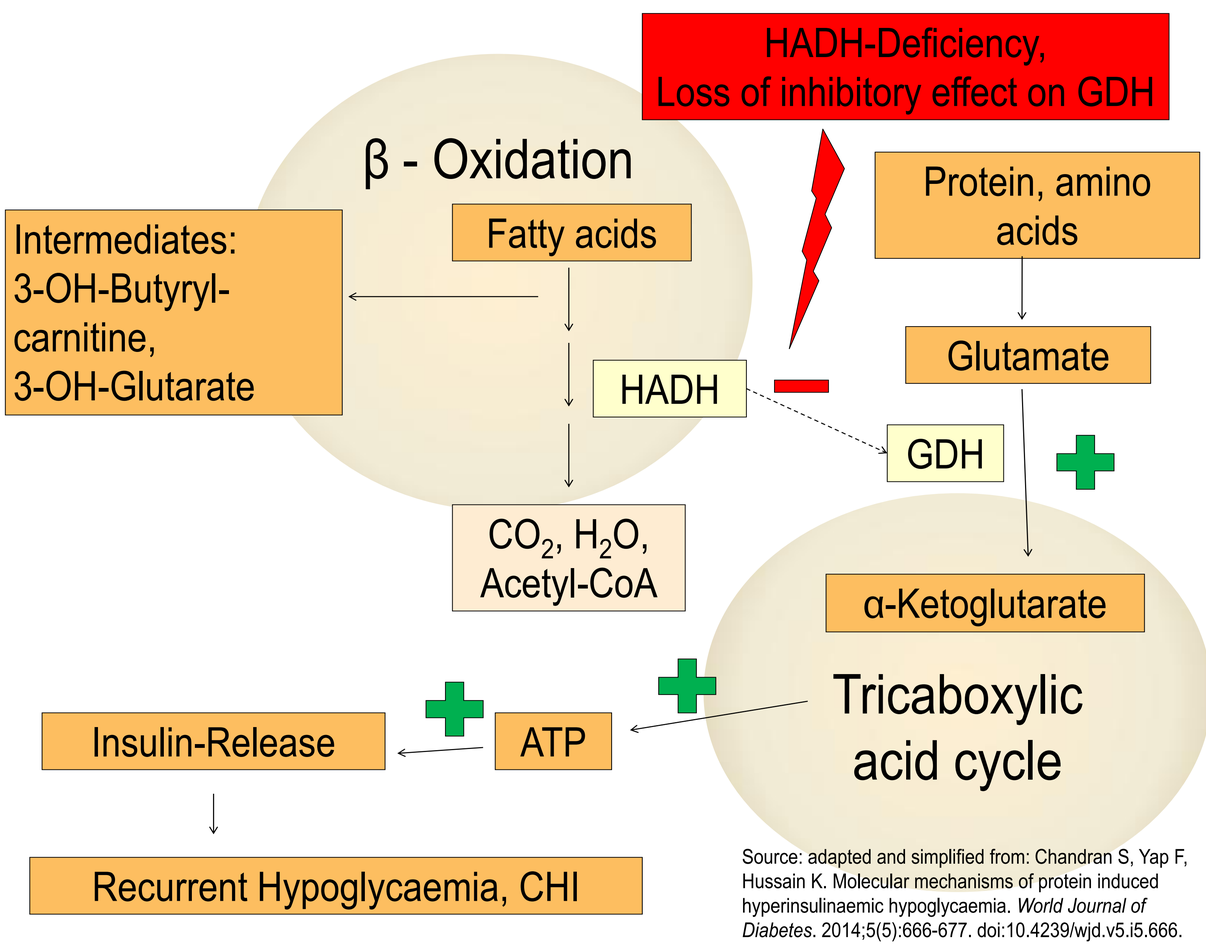
Two patients with *HADH* (SCHAD) Hyperinsulinism in part without detectable 3-Hydroxybutyrylcarnitine/ 3-Hydroxyglutarate

Susanne Weiss[1], Nadine Bachmann[2], Ertan Mayatepek[1], Carsten Bergmann[2], Thomas Meissner[1], Sebastian Kummer[1]
[1]Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Duesseldorf, Germany,
[2]Bioscientia Center of Human Genetics, Ingelheim, Germany

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-Hydroxylacyl-CoA dehydrogenase (*HADH/SCHAD*) deficiency. This disorder is usually characterized by an accumulation of 3-hydroxybutyrylcarnitine in plasma and 3-hydroxyglutarate in the urine.

Pathophysiology in beta cells of patients with HADH CHI



Source: adapted and simplified from: Chandran S, Yap F, Hussain K. Molecular mechanisms of protein induced hyperinsulinaemic hypoglycaemia. *World Journal of Diabetes*. 2014;5(5):666-677. doi:10.4239/wjd.v5.i5.666.

Patients: clincial presentation

Two patients of turkish origin, consanguineous parents.
Patient 1: male, 17 years, postnatal macrosomy, recurrent hyperinsulinaemic 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 hyperinsulinaemic 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.

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

Age	Sex	Gene	Mutation	Biochemical Analysis
17 J	m	**HADH**	HOM c.428T>A (p.Ile143Asn), new mutation	no detection of significant concentrations of 3-OH-Butyrylcarnitine or 3-OH-Glutarate.
9 J	w	**HADH**	HOM c.706C>T (p.Arg236*) mutation published before[1]	no analysis.

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:

1. Di Candia, et al.: Identification of a diffuse form of hyperinsulinemic hypoglycemia by 18-fluoro-l-3,4 dihydroxyphenylalanine positron emission tomography/CT in a patient carrying a novel mutation of the *HADH* gene *Eur J Endocrinol 160 (6) 1019-1023*
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4. *OMIM Database: http://www.omim.org/entry/601609, retrieved 26.08.2016*

Correspondence: susanne.weiss@med.uni-duesseldorf.de. No conflict of interest.

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Susanne Weiss
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