Transient Hyperinsulinaemic Hypoglycaemia in Association with a Novel ABCC8 Mutation: Expanding the Clinical Phenotypes

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BACKGROUND
- Hyperinsulinaemic hypoglycaemia (HH) results from unregulated insulin secretion from pancreatic β-cells.
- Hyperinsulinaemic hypoglycaemia (HH) can be transient or permanent.
- Transient HH (spontaneous resolution of HH within few weeks) is associated with intrauterine growth restriction, maternal diabetes, erythroblastosis fetalis etc.
- Transient HH has not been reported with ABCC8/KCNJ11 mutations, which are the commonest cause of HH.

OBJECTIVE
Molecular characterization of a novel ABCC8 mutation associated with a transient HH phenotype seen in a family with two affected cousins.

METHODS
- Site-directed mutagenesis was used to create the ABCC8 point mutation in pcDNA3.1-hamster SUR1 cDNA construct.
- HEK293 cells were transfected with WT/mutant hamster SUR1 cDNA and WT mouse Kir6.2 cDNA using FuGENE.
- Functional properties of channels were studied using whole-cell patch-clamp recordings.
- After attaining whole-cell configuration, cells were voltage-clamped.
- The voltage-clamp protocol consisted of a holding potential of -80 mV, after which the cells were ramped from -150 mV to 50 mV over 1 second (200 mV/s) and then stopped back to -80 mV.
- Cells were superfused with 5 K+ bath solution (CNT), followed by 100 μM DZK to activate KATP currents, and 100 μM DZK and 100 μM Tolbutamide (DZK+TOL) to inhibit KATP currents.
- Both homogenous and heterozygous expressions of the mutants were studied.

RESULTS
A, B, C: Graph showing mean pA/pf for Wild type (WT), T1516M SUR1 and Heterozygous T1516M SUR1 KATP Channels at +40 mV. Data was analyzed using Wilcoxon matched-pairs signed rank test. D, E, F: Representative trace from whole-cell patch-clamp recordings for cells expressing WT, T1516M SUR1 and Heterozygous T1516M SUR1 KATP Channels. G: Graph showing KATP current at +40 mV from HEK293 cells transfected with cDNA of mouse Kir6.2 along with cDNA of WT SUR1, T1516M SUR1 Mutant and 1:1 ratio of WT and T1516M SUR1 Mutant. Data is presented as Mean ± SEM, and was analyzed using Mann-Whitney test, p = 0.28 (not significant [ns]), n = 7-12 cells.

CONCLUSIONS
- This study expands the clinical phenotypes reported with ABCC8 mutations.
- Molecular characterization was consistent with the observed clinical phenotypes.

The authors have nothing to disclose