Congenital hyperinsulinism diagnosed in childhood can have a monogenic aetiology

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INTRODUCTION

- Congenital Hyperinsulinism (HI): a monogenic disorder characterised by inappropriate insulin secretion despite low blood glucose.
- Commonly diagnosed in infancy (<12 months), high birth weight is often a feature.
- Characteristics of childhood HI diagnoses (>12 months) are not well studied.

AIM

1. Compare prevalence, clinical and genetic features of HI diagnosed in childhood to infancy.
2. Determine if childhood diagnoses are driven by ascertainment or true later disease onset.

METHOD

HI referrals genetically tested using targeted sequencing, **n = 2058**

- Infancy (<12 mnths) **n = 1885**
- Childhood (12 mnths-16 years) **n = 173**

Comparisons for 3 most common childhood genetic causes:
- Prevalence, clinical and genetic features

RESULTS

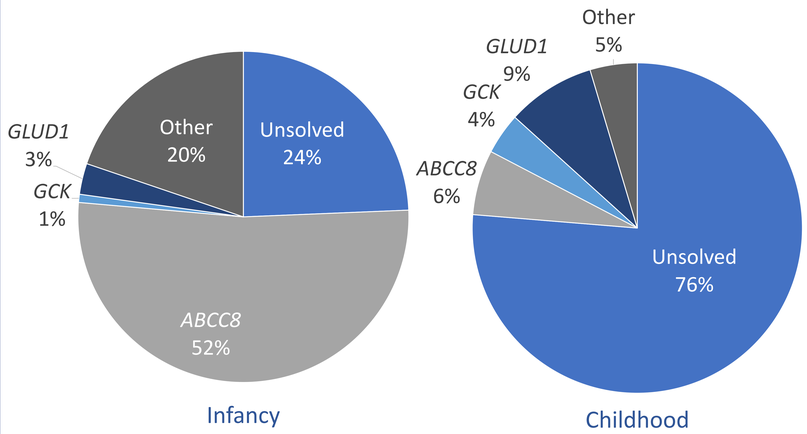

Figure 1: Pie-charts showing the results of genetic analyses for patients diagnosed in infancy (left) and those diagnosed in childhood (right).

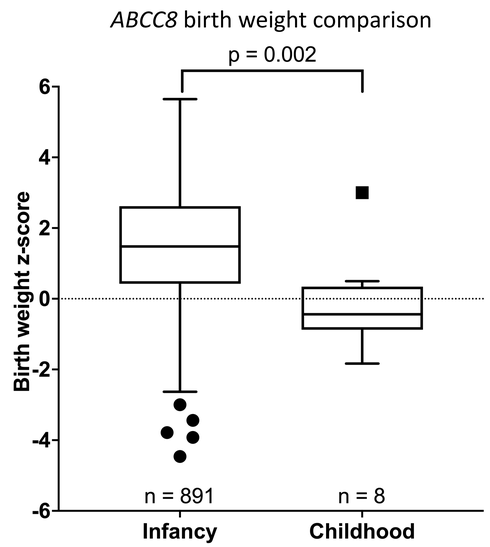

Figure 2: A box and whisker plot of birth weight z-scores corrected for gestational age for patients diagnosed in infancy and in childhood with ABCC8 mutations. Patients diagnosed in infancy had a significantly higher median birth weight than those diagnosed in childhood. P = 0.002, Mann-Whitney.

- **A genetic cause was identified for 41/173 (24%) of Exeter referrals diagnosed with HI in childhood,** compared to 76% of infancy diagnoses (Figure 1).
- Mutations were identified in 8 different genes for childhood diagnoses, with *ABCC8*, *GCK* and *GLUD1* being the most common (n = 33/41).
- Significantly lower median birth weight z-score for childhood diagnoses with *ABCC8* mutations (-0.44), compared to infancy diagnoses (1.5) (Figure 2).
  - Lower birth weight suggests these may be true childhood disease onset.
- A novel genotype-phenotype correlation for *GLUD1*-HI, those diagnosed in childhood more likely to have mutations in the catalytic domain (73%) of the enzyme than the allosteric domain (27%) (Figure 3).
  - Indicating a true later disease onset for childhood *GLUD1* diagnoses.
- For *GCK*-HI, 86% (6/7) of childhood diagnoses had mutations also identified in infancy diagnoses. Both cohorts had a similar median birth weight.
  - Suggesting ascertainment is also a factor for childhood diagnoses.

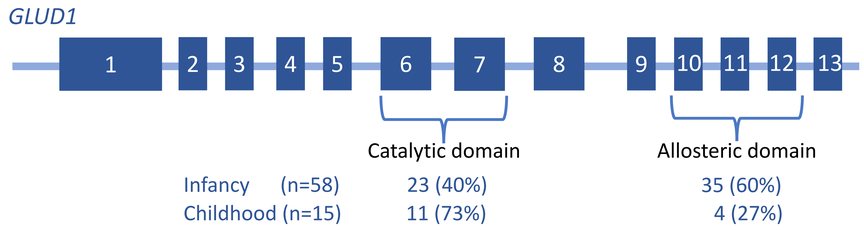

Figure 3: Diagram depicting the exons of GLUD1 and the locations of the catalytic and allosteric domains. The association is statistically significant, P = 0.04, Fisher's exact test.

CONCLUSIONS

HI diagnosed in childhood can be monogenic.

Childhood diagnoses are driven by both ascertainment and true later disease onset.

- Evidence of true childhood disease onset for *ABCC8*-HI.
- Novel genotype-phenotype correlation for *GLUD1*-HI indicates a link between mutation site and age at diagnosis.
- Evidence of ascertainment issues for *GCK*-HI.

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