CONGENITAL HYPERINSULINISM DIAGNOSED IN CHILDHOOD CAN HAVE A MONOGENIC AETIOLOGY

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INTRODUCTION

1. Congenital Hyperinsulinism (HI): a monogenic disorder characterised by inappropriate insulin secretion despite low blood glucose.
2. Commonly diagnosed in infancy (<12 months), high birth weight is often a feature.
3. 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

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<tr>
<th>HI Referrals</th>
<th>Infancy</th>
<th>Childhood</th>
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<tbody>
<tr>
<td>(&lt;12 mnths)</td>
<td>n = 15</td>
<td>n = 173</td>
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<tr>
<td>(12 mnths-16 yrs)</td>
<td>n = 58</td>
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Comparisons for 3 most common childhood genetic causes:
- Prevalence, clinical and genetic features

RESULTS

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.

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.

CONCLUSION INFORMATION

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