

# Longitudinal Auxological Recovery and Reduced Neurodevelopmental Problems in Patients with Congenital Hyperinsulinism

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## Background:

- Congenital Hyperinsulinism (CHI) is the most common cause of severe and recurrent hypoglycaemia in childhood.
- CHI can be categorised as focal or diffuse disease.
- There are few descriptions of the natural history of CHI and most follow up studies have focused on neurodevelopmental outcomes and time to resolution.
- Most studies focus exclusively on genetically confirmed CHI despite evidence that neurological outcomes are just as devastating in those with non-genetic, transient disease<sup>1</sup>.
- Other than descriptions of increased birth weight, there is little descriptive work on the auxology of patients with CHI.
  - A few studies allude to normal height<sup>2</sup> and growth rate<sup>3</sup> but without providing longitudinal data.

## Aims:

1. Review longitudinal auxology of patients with CHI
2. Review outcomes of disease resolution and neurodevelopmental status in a longitudinal cohort of patients with CHI
3. Assess diazoxide as a prognostic marker for CHI

## Methods:

- All patients treated for CHI in our centre over a three-year period from 2011 to 2013 were included if hyperinsulinism persisted beyond 4 weeks.
  - Those secondary to gestational diabetes were excluded.
  - Resolution was defined as having undergone an age appropriate fast off medication with no hypoglycaemia.
- Height, weight and medication were reviewed at 6-12 monthly intervals until 60 months of age.
- Neurodevelopmental problems were classed as none, some or severe and were assessed at 60 months of age.
- Standard Deviation Scores (SDS) were calculated for height and weight.

## Patient characteristics:

- Seventy patients with confirmed CHI were enrolled into the study. Natural history outcomes are shown in Fig 1.
  - 68 (97%) were diagnosed in the neonatal period with fourteen (20%) demonstrating genetic mutations.
  - Six patients underwent curative lesionectomy and two required subtotal pancreatectomy
  - Mean insulin at diagnosis was 73pmol/L at a plasma glucose of 1.6mmol/L (29mg/dL)
  - All patients received diazoxide as a first line treatment.

## Results:

### Auxology profiles:

- Ten patients were excluded from longitudinal weight analysis and 18 from height analysis due to insufficient measurements.
- **Mean weight SDS was -1.00 at birth with a dip to -1.27 at 3 months and subsequent recovery (Fig 2)**
  - Mean weight SDS was -3.2 in Small for Gestational Age (SGA) patients and +0.4 in non-SGA patients
    - Genetic status had no impact on birthweight in non-SGA patients (P = 0.098)
- **Mean height SDS was -1.5 at 3 months, rising to -0.06 SDS and subsequently remaining stable (Fig 3)**

### Neurodevelopmental outcomes:

- At five years **only 11 patients (15%) had neurodevelopmental delay**
  - This was mild in 10 patients (mild cognitive delay or learning difficulties) and severe in one patient.
  - Neither genetic status nor focal vs diffuse CHI had any impact upon neurodevelopmental outcomes.

### Diazoxide as a prognostic marker:

- Mean initial diazoxide dose (mg/kg/day) was higher in those with persistent vs transient disease at 6 months (8.0 vs 5.6, P = 0.007) and 5 years (9.4 vs 6.4, P = 0.015).
- **A cut-off maximum dose of diazoxide of >5mg/kg/day vs <=5mg/kg/day showed good prediction for persistent disease:**
  - At 6 months 62% vs 32%, P = 0.015
  - At 5 years 27% vs 7%, P = 0.02

### Resolution of CHI

- Spontaneous resolution was achieved in:
  - 19 patients (27%) by 3 months of age
  - 60 patients (86%) by 5 years of age
- Seven of eight patients who underwent surgery achieved resolution
- **Those born SGA had a lower chance of persistent disease:**
  - At 6 months (29% vs 38%, P = 0.009)
  - At 5 years (0% vs 23%, P = 0.12)

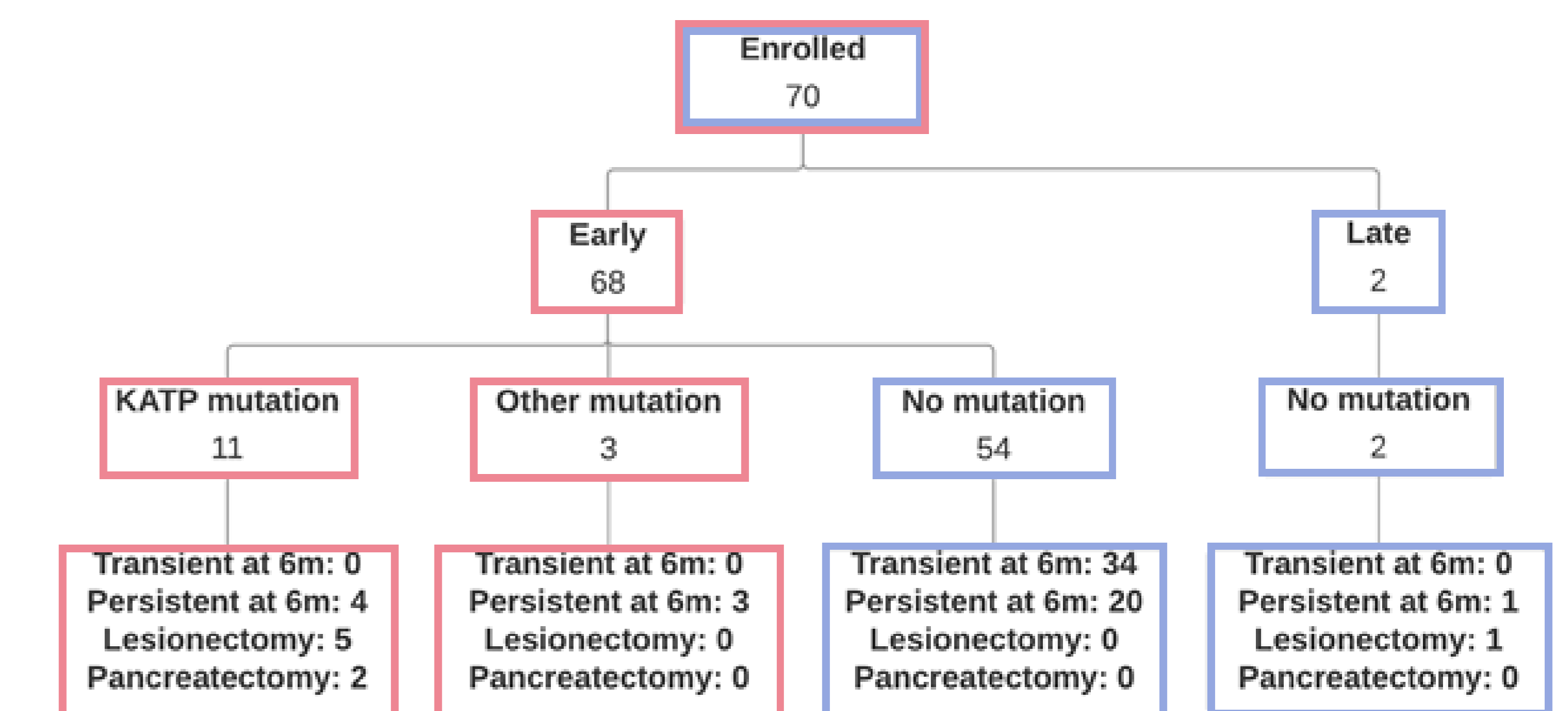


Figure 1. Flowchart of natural history outcomes of CHI.

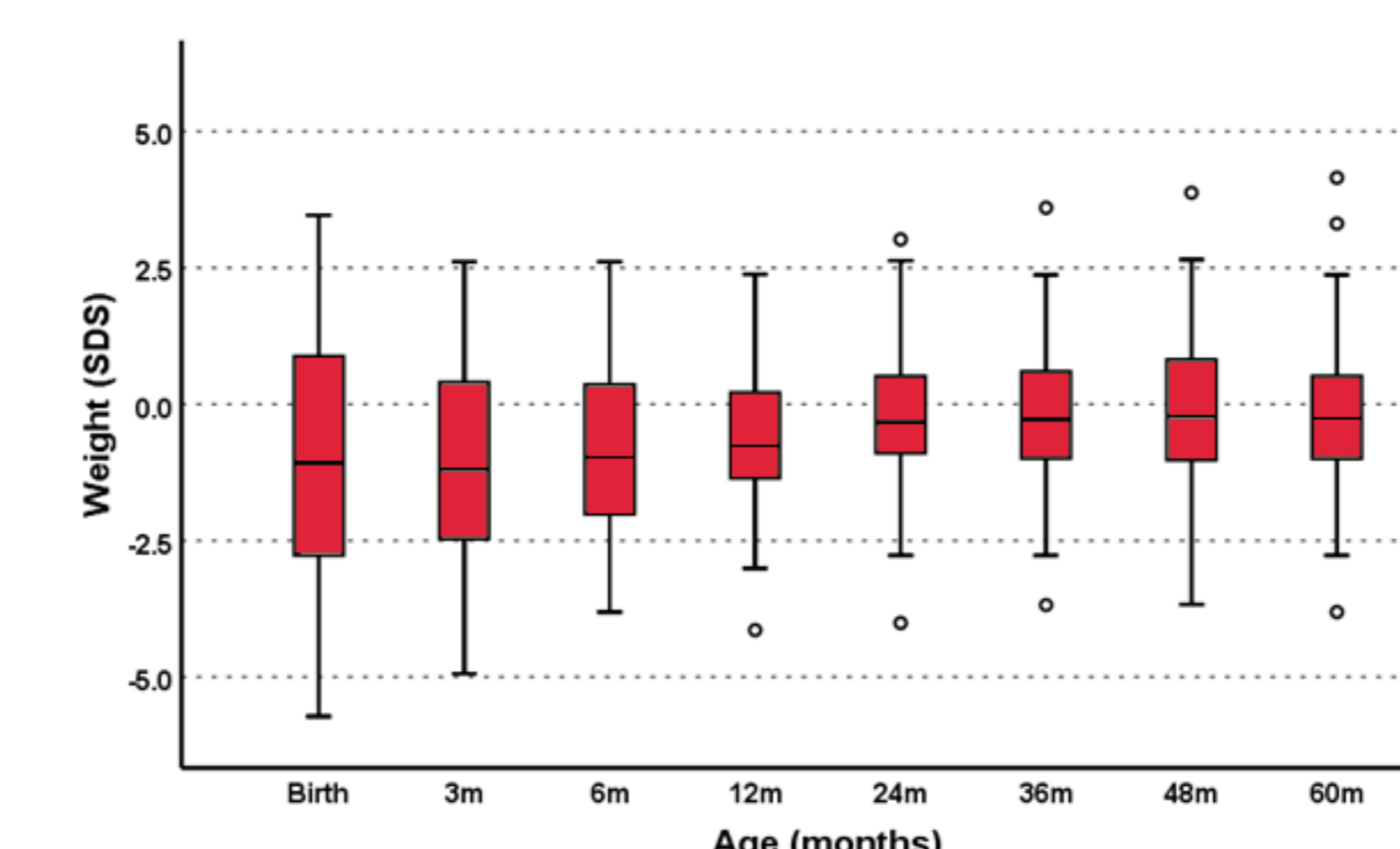


Figure 2. Box and whisker plot of median weight SDS by age.

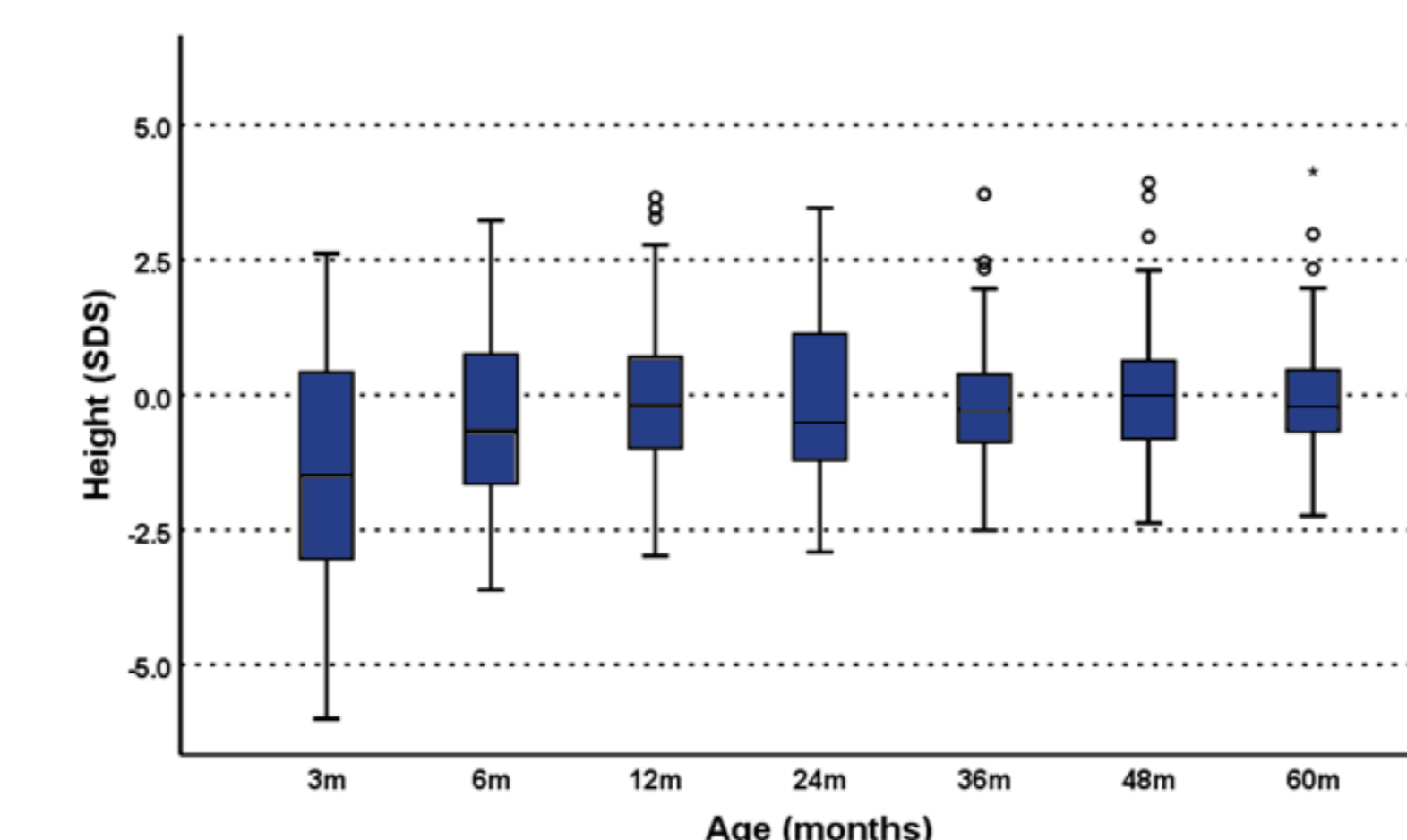


Figure 3. Box and whisker plot of median height SDS by age.

## Discussion:

- We have provided the first report of the natural history of CHI with regards to auxology and medication.
- Contrary to typical descriptions of CHI patients being born large for gestational age, we found an appropriate birth weight (+0.4 SDS) in those not SGA.
- In the context of often supraphysiological glucose requirements we did not see excessive weight gain in our patient cohort.
- Height was very well preserved in CHI patients indicating that early life management does not impact upon growth.
- Our cohort had a very low level of neurodevelopmental problems. While this may be due to a high number of transient cases, previous studies do not suggest this is protective<sup>1</sup>.
- In the absence of disease severity markers, predicting outcomes can be very challenging.
  - We have shown that a maximum dose of diazoxide <=5mg/kg/day as well as being born SGA are positive prognostic factors and predict disease resolution at both 6 months and 5 years.

## References:

1. Avatapalle et al. Front Endocrinol. 2013. doi 10.3389/fendo.2013.00060
2. Mazor-Aronovitch et al. Eur J Endocrinol. 2007. doi 10.1530/EJE-07-0445
3. Su et al. Horm Res Paediatr. 2014. doi 10.1159/000356911