Clustering of Hypoglycaemia Events in Patients with Hyperinsulinism (HI): Extension of the Digital Phenotype

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Background:

- Hyperinsulinism (HI) is the most comon cause of severe and recurrent hypoglycaemia in childhood.
- High cerebral glucose utilisation overnight, combined with dysregulated insulin secretion, results in a theoretically high risk period for these patients in the early hours[1].
- Recent descriptions of a digital phenotype include data derived from digital sources such as Continuous Glucose Monitoring (CGM)[2].
- This digital phenotype would provide information on the timing of hypoglycaemia events and allow for more targeted interventions to prevent hypoglycaemia.

Aims:

1. Extend the digital phenotype of HI by describing the timing of hypoglycaemia events.
2. Establish a basis upon which future work can provide targeted behavioural change to prevent hypoglycaemia.

Methods:

- Patients underwent CGM with a Dexcom G4 or G6 as part of their clinical assessment for HI.
- A comparitor group of patients with Idiopathic Ketotic Hypoglycaemia (IKH) also underwent CGM.
- CGM data was analysed using bespoke computer code to describe temporal and weekly trends in hypoglycaemia.
- A hypoglycaemia event was defined as at least three consecutive CGM values <3.5mmol/L (63mg/dL).

Patient characteristics:

- CGM data totalling 150,000 minutes was captured from 23 patients with HI with a mean age of 57 months.
- Similar data volumes were obtained from IKH patients.
- No sex differences were found between HI and IKH groups but HI patients were younger than IKH patients as expected (mean age 57 months vs 82 months, P = 0.03).

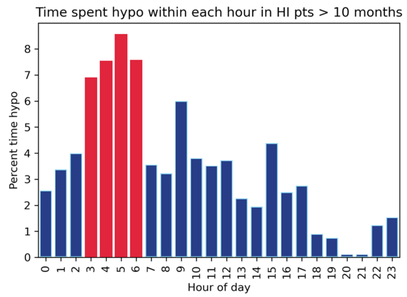

Figure 1

Time spent hypo within each hour in IKH pts

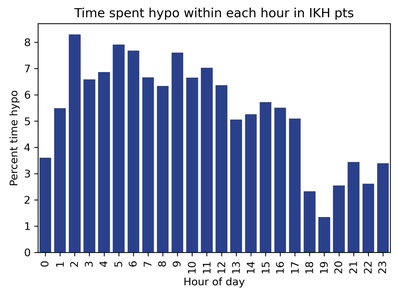

Figure 2

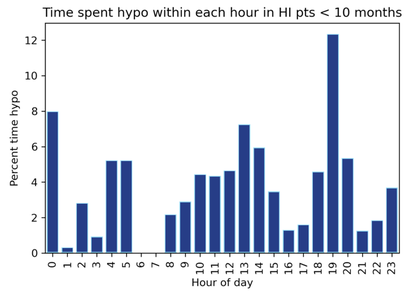

Figure 3

Results:

Description of hypos in those with HI

- There were 108 hypoglycaemia events over 149 days (1.4 hypos per day).
- Time spent in hypoglycaemia was 4991 minutes (3.3 % of the time).
- Mean hypo length was 46 minutes and there were 47 hypos lasting more than 30 minutes.

Timing of hypoglycaemia events:

- In CHI patients > 10 months of age, **hypoglycaemia events are not spread evenly or randomly throughout the day but are concentrated in the early hours of the morning** (Figure 1).
  - In the early hours, between 0300 and 0700H, 7.6% of time was spent in hypoglycaemia compared with 2.6% of time outside this period.
- This same pattern was less pronounced in IKH patients (Figure 2) and not seen at all in CHI patients < 10 months of age (Figure 3).
- An increased early hours tendency to hypoglycaemia was seen in those with a CHI genetic mutation vs those without, in those CHI patients not receiving medication vs those on treatment and as hypoglycaemia thresholds were reduced to 3.0 and 2.6mmol/L[3].

Hypoglycaemia throughout the week:

- On further analysis of patient data, it is clear that **the risk of hypoglycaemia in the early hours is not the same on every day of the week**.
- The increased risk seen in the early hours is concentrated on Fridays and Saturdays (Figure 4).
- On **Saturday 0300-0700H, patients spent 12.5% of time hypoglycaemic**
  - Over 50% more than any other 4 hour period except Friday.
- Overall on Saturdays, patients spent 5.7% of time hypoglycaemic
  - Over 50% more than any other day except Friday.

Discussion:

- We have, for the first time, described the timing of hypoglycaemia events in patients with HI and thus extended the digital phenotype.
- Hypoglycaemia is not evenly or randomly spread throughout the day but is in fact concentrated in the early hours of the morning, likely due to overnight fasting, high cereral glucose utilisation and minimal blood glucose checking and impaired awareness while asleep.
- Patients < 10 months old have minimal routine and thus less predictable hypos.
- This pattern may be unique to HI as the tendency is less in those with IKH, those without genetic mutations and those not receiving HI medication[3].
- Weekly patterns of hypoglycaemia are not yet fully understood but are likely somewhat related to the behavioural routines of parents.
- **These findings lay the foundations for the digital phenotyping of individual patients and families and subsequent targeted behavioural interventions to proactively prevent hypoglycaemia at times of risk.**

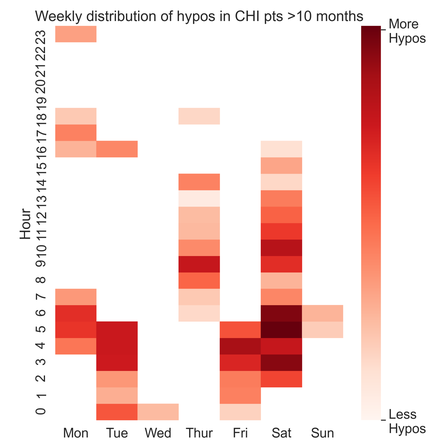

Figure 4

References:

1. Kalsbeek A et al. Mol Metab. 2014. doi:10.1016/j.molmet.2014.03.002
2. Jain SH et al. Nat Biotechnol. 2015. doi:10.1038/nbt.3223
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