Neonatal hyper- and hypoglycaemia;
Widening the clinical phenotype of Transient Neonatal Diabetes Mellitus due to 6q24 methylation defects.

Tashunka Taylor-Miller[1], Michele O'Connell[1,2], Matthew Sabin[1,2]
Departments of Endocrinology & Diabetes (1) Murdoch Children's Research Institute (2) Royal Children's Hospital, Melbourne, AUSTRALIA
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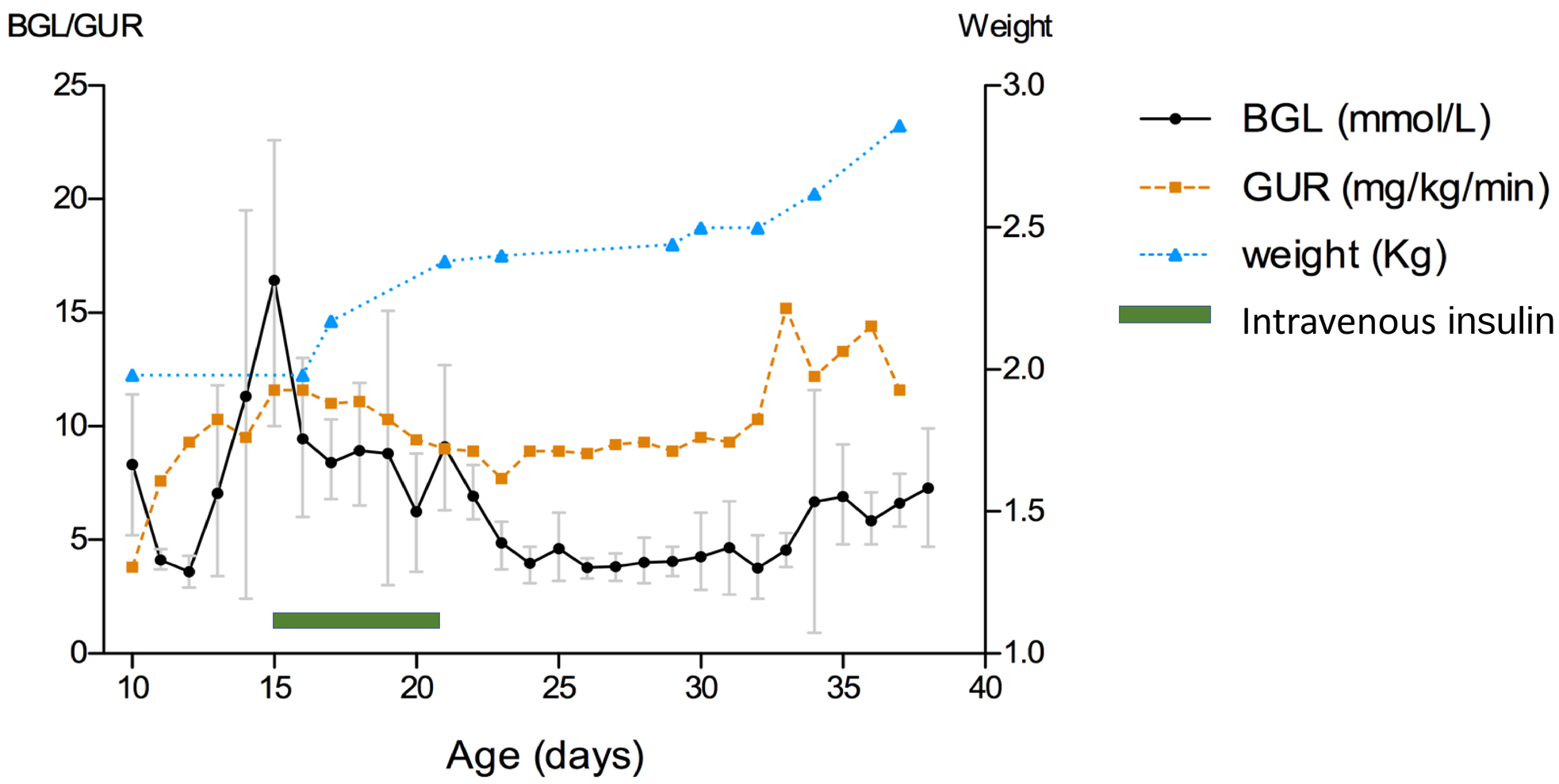
Clinical Case Presentation

- Term male, birth weight 2.1kg.
- BGL 1.8mmol/L at 1.5 hours of life, resolved with oral formula and intravenous dextrose.
- **Day 9** life **hyperglycaemic** BGL 22.7mmol/L on normal breast milk feeds 160 ml/kg/day. Fluctuating hyper-normoglycaemia conservatively monitored; nadir BGL 2.9mmol/L on day 12 [See graph 1].
- Day 15, intravenous insulin infusion commenced for persistent hyperglycaemia (range BGL 15-22.6mmol/L).
- Insulin weaned over next 6 days and ceased day 21 following 48 hours of normoglycaemia (GUR 9mg/kg/min).
- **Day 30 non-ketotic hypoglycaemic** BGL 2.8mmol/L (GUR 9.3-9.5) with inappropriately recordable insulin 1.2mU/L.
- Sporadic hypoglycaemia continued.
- Normoglycaemia achieved on large-volume breastmilk feeds 280 ml/kg/day, (peak GUR 15.2mg/kg/min).
- Ongoing symptomatic hypoglycaemia from 1 to 22months of age; presenting as irritability, floppiness, mood changes. Unrelated to intercurrent illness or protein-rich meals[1].
- Normoglycaemia continues to be achieved with enteral supplementation. Episodic hypoglycaemia BGL <2.8mmol/L has been managed orally.

Graph 1. Trend of Blood glucose level (BGL), weight and glucose utilisation rate (GUR)



Genetic Diagnosis

- KCNJ11, ABCC8 and INS gene mutations excluded.
- Methylation-specific analysis of chr 6 therefore undertaken, identifying paternal uniparental disomy 6q24 (**UPD6pat**) and confirming TNDM.
- Variation in timing and duration of hyper- and hypo-glycaemic episodes is described in patients with 6q24 methylation defects.

Hypoglycaemia in TNDM

Hypoglycaemia in 6q24 TNDM

- First reported hypoglycaemia-pheotype in 2013 following diabetes-phase remission in 6q24 TNDM, prevalence 14% (6 out of 43 patients)[2].
- Hypoglycaemia (blood glucose <2.6 mmol/L) was diagnosed at a median age of 8months of age, which was within 2–22 weeks of diabetes-phase remission.
- UPD6pat is most common genetic mutation (5 out of 6).
- Presentation of hypoglycaemia varied: noted incidentally on routine bloods within the context of intercurrent viral illness, also symptomatic lethargy and shakiness which improved with feeding.
- UPD6pat morely likely to require overnight bolus feeds and diazoxide treatment of hypoglycaemia, compared to the paternal duplication who had episodic hypoglycaemia.
- Mechanism onset and resolution remain unknown.

Take Home Points

- **Methylation defects chromosome 6q24 are the most common cause of Transient Neonatal Diabetes Mellitus (TNDM).**
- **Onset of diabetes-phase usually within first week of life, resolution often at 4 months of life.**
- **Paternal uniparental disomy (UPD6pat) is most common, associated with increased incidence of extra-pancreatic congenital anomalies and hypoglycaemic phenotype after diabetes remission.**

References:
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