HNF4A MUTATION: a roller coaster of hyperinsulinism and diabetes

The Pennine Acute Hospitals NHS Trust

Dr Thomas Webster, Paediatric Registrar, Pennine Acute Hospitals NHS Trust

Dr Anindya Mukherjee, Consultant Paediatrician with an interest in diabetes, Pennine Acute Hospitals NHS Trust

Dr Sarah Ehtisham, Consultant Paediatric Endocrinologist, Central Manchester University Hospitals NHS Foundation Trust, Honorary Lecturer University of Manchester

Learning objectives

To highlight the need to investigate, in detail, all neonates with persistent hypoglycaemia in order to reach a diagnosis, inform the management and to help provide information regarding prognosis

To report the ongoing investigation of a patient with heterozygous HNF4 alpha mutation with deranged liver function tests and hepatosplenomegaly

To demonstrate the burden of illness that can arise from a single genetic abnormality

Initial presentation

37+4 weeks gestation – normal delivery

4.4 kg (98th centile)

Mum – previously well, pregnancy induced hypertension

Normal examination, no dysmorphic features

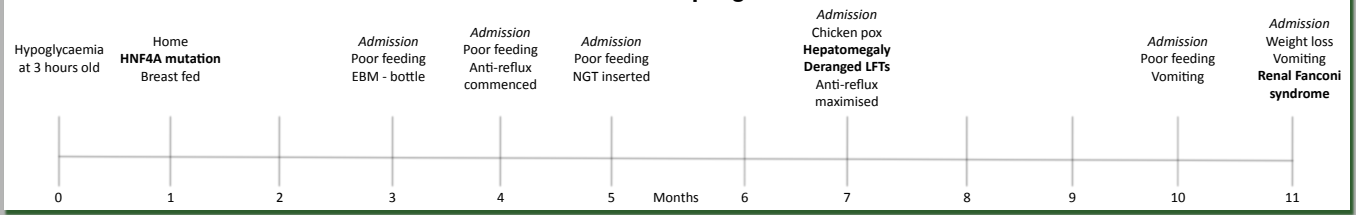
Blood sugar at 3 hours old – 0.7 mmol/l

Jittery and sweating, no seizures

Anti-hypoglycaemic management escalated to keep blood sugar above 3.5 mmol/L

- 18 mg/kg/minute glucose
- Glucagon 30 micrograms/kg/hour
- Oral hydrocortisone 1mg/kg qds
- Two stat doses of hydrocortisone 5 mg IV

Timeline of progress



Tertiary management and diagnosis

Transferred to tertiary endocrine unit at 2 days old

Hyperinsulinaemia confirmed
Insulin 20 mU/l, c-peptide 1510 pmol/l

Genetic screen performed – heterozygous mutation of HNF4A

Medicines weaned – discharged home at 1 month old on diazoxide 2.5 mg BD

Progress

Multiple presentations

3/12 old – poor feeding and dehydration

4/12 old – poor feeding, vomiting, commenced anti-reflux treatement

5/12 old – poor feeding, vomiting

8/12 old – chickenpox, deranged LFTs, hepatosplenomegaly

10/12 old – poor feeding, vomiting

Feeds

At d/c – breast feeding 4 hourly

Struggled to maintain volumes – 3/12 old bottle fed EBM + polycal

Poor feeding and falling centiles – NGT introduced

7-8/12 old – effortless vomiting, weight loss. Refusing all milk orally. Some solids.

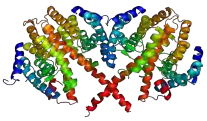
Barium swallow – normal

Trial of hydrolysed milk then amino acid formula – still vomiting

Vomiting causing stress

-Physiological stress – falling sugars

-Psychological stress – anxiety around feed times



HNF4A Protein

Hepatomegaly

Liver function tests normal perinatally

9/12 old – chickenpox – noted to have raised ALP and ALT with palpable hepatosplenomegaly

Comprehensive liver screen unremarkable

USS Liver - course nodular echotexture

Awaiting liver biopsy

Renal involvement

Hyponatraemic from birth – resolved

Screened at 10/12 old during prolonged admission for weight loss and poor feeding – confirmed renal Fanconi syndrome

Renal USS normal – no calcinosis

New implications

- Burden of oral medicines – extra supplements
- Effect on weight – renal protein loss

Hepatocyte nuclear factor 4 alpha mutation

A member of the nuclear receptor family of transcription factors - abundant in liver

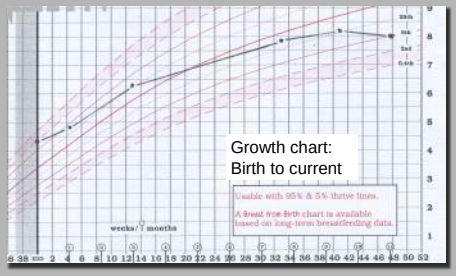
Heteroxzygous mutations cause hyperinsulinaemic hypoglycaemia in infancy
- Likely to resolve

Predisposes to maturity onset diabetes of the young (MODY)
- Needs lifelong screening for diabetes

Predisposes to renal Fanconi syndrome with hypophosphataemic rickets
- Regular renal screening

Literature consists of recent case-reports - long term prognosis difficult to predict

Association with hepatosplenomegaly rare



References

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