From Hypoglycemia to Hyperglycemia

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INTRODUCTION

Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes characterized by autosomal dominant inheritance, a young age of onset and pancreatic β-cell dysfunction. Dominant inactivating mutations in HNF1A and HNF4A have been described to cause hyperinsulinism before evolving to diabetes.

OBJECTIVES

We reported a case of HNF4A monogenic diabetes.

METHODS

Clinical data were obtained from chart review. All coding regions in the HNF4A transcript (pancreatic-specific) and the corresponding pancreatic promoter regions were sequenced by the Sanger method.

RESULTS

A full-term baby girl was born by vacuum extraction with birth weight of 2.75 kg (10th – 25th percentile). Perinatal course was uneventful in particular there was no history of gestational diabetes. She was admitted to nursery on day 4 for neonatal jaundice and poor feeding. Physical examination was unremarkable. Blood glucose was 0.6 mmol/l upon admission and urine ketone was negative. Electrolytes and blood gas were normal. Glucose infusion rate of 11 mg/kg/min was needed to maintain normal glucose level. Critical samples revealed insulin of 42 mIU/L while other investigations including cortisol, growth hormone, ammonia and metabolic workup were normal.

RESULTS

Diagnosis of hyperinsulinemic hypoglycemia was made. Diazoxide at 5 mg/kg/day was started together with hydrochlorothiazide. It was further titrated up to 7 mg/kg/day and intravenous dextrose could be taken off. Full enteral feeding was established with diazoxide and hydrochlorothiazide. The baby was discharged on day 42 with home blood glucose monitoring.

Regular follow up was arranged. Normal glucose level was maintained with the same dose of diazoxide while the child grew. At 3.5 months, blood glucose was noted to be high at 11.5 mmol/l. She was admitted for trial of stopping diazoxide. It was successfully weaned off while blood glucose level remained normal. She was regularly followed up for growth and development. At 4.5 years, she was noted to have language delay, rigid and hyperactive behavior. She was assessed in Child Assessment Service, Clinical Psychology and Child Psychiatry and diagnosed attention deficit hyperactivity disorder, Asperger's syndrome, specific learning disorder with low average intelligent quotient. As she had low mood and marked anxiety symptoms, she was put on atomoxetine and sertraline.

At 17 years, she presented to another hospital with 2 week history of polyuria and polydipsia. Physical examination was unremarkable in particular there was no acanthosis nigricans. Her body weight was 42.8 kg (3rd – 10th percentile), body height was 146.5 cm (<3rd percentile), and body mass index was 19.9 kg/m2. Blood glucose was 17.1 mmol/l and urine ketone was 4+ at emergency room. Repeated blood glucose was 19.1 mmol/l and blood β-hydroxybutyrate was 0.5 mmol/l at paediatric unit. Blood gas showed pH 7.38 and bicarbonate 21 mmol/l.

RESULTS

After 2 hour of rehydration with normal saline, blood glucose was still high at 16.4 mmol/l and urine ketone was moderate. She was then put on multiple daily insulin injections at 0.8 unit/kg/day. Later A1c came back to be 13.5%, insulin was 3.8 mIU/L and anti-islet cell antibody was negative. In view of past history of congenital hyperinsulinism, HNF4A +/- HNF1A mutational analysis was arranged. Sanger sequencing revealed heterozygous HNF4A mutation at c.1001_1004dupAGTT p.(Phe335Leufs*12). It was a novel frameshift variant which was absent from normal controls. It was predicted to create a premature stop codon. In view of the positive mutational analysis, the girl was switched from insulin to gliclazide. Glycemic control was satisfactory after switching to suphonylurea and latest A1c was 6.7%. Both parents' and younger sister's fasting glucose and A1c were normal at the time of investigation. Mother carried the same mutation while father and younger sister carried no mutation.

CONCLUSIONS

The case demonstrates that mutation in HNF4A can cause hyperinsulinism early in life and diabetes later. Given the heterogeneous clinical phenotypes, all children with transient, diazoxide-responsive hyperinsulinism without clear etiology should be screened for HNF1A and HNF4A mutations at it predicts the clinical course and affects the subsequent management.

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57ESPE 180--P3

Fetal, neonatal endocrinology and metabolism (to include hypoglycaemia)

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Poster presented at: 57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018

PosterSessionOnline.com