



Concurrent hyperinsulinism and hypopituitarism in a 22 month old child due to a novel FOXA2 mutation

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INTRODUCTION

FOXA2 is a transcription factor involved in the development of the gut, pancreas, and pituitary gland.

Co-existence of congenital hypopituitarism and congenital hyperinsulinemia is extremely rare, and only a few cases with FOXA2 mutation have been reported in the literature.

While homozygous mutations are incompatible with life, syndromic hypopituitarism and hyperinsulinemia can be seen in heterozygous mutations.

We present a case of congenital hypopituitarism and hyperinsulinemic hypoglycemia with a novel FOXA2 mutation.

CASE REPORT

A 22-month-old girl was referred to pediatric endocrinology due to short stature. She was the first child of healthy, non-consanguineous parents with no relevant family history. Delivery was by Cesarean section at 40 weeks gestation. Birth weight and length were 3600 grams (76 percentile) and 48 cm (26 percentile), respectively. At the age of two days, she had an episode of hypoglycemia requiring hospitalisation for 10 days. Her family reported stalled development from the age of nine months and she had a further three episodes of hypoglycemia, but no endocrinological evaluation was performed. Her father had growth hormone deficiency at 10-years- old requiring growth hormone treatment until 16-years-old.

On initial examination, height was 75 cm (-2.76SD) and weight was 8.6 kg (-2.15SD), while mid parental height was 158 cm (-0.87SD). She had no dysmorphic features.

Complete blood count, liver and kidney function tests were normal. She had a low free-thyroxine (0.57ng/dL) but thyroid stimulating hormone was normal (2.09 µl/mL).

Plasma glucose was 36 mg/dL and concurrent plasma insulin was 2.96 u/mL and C-peptide was 1.15 ng/mL. Hypoketotic hypoglycemia was confirmed by repeated measurements. Glucagon stimulation test resulted in a rise in plasma glucose to 102 mg/dL. Both cortisol (6.99 mcg/dL) and growth hormone (0.16 ng/mL) response to hypoglycemia was blunted. Ammonia, lactate, b-hydroxybutyrate and non-esterified free fatty acid levels were normal or suppressed. After hospitalization, glucose infusion and diazoxide was started. She had cortisol response (21 mcg/dL) to low dose adrenocorticotropin stimulation test. Levothyroxine (25mcg-day) was started. When euthyroid, growth hormone stimulation test was performed with L-dopa, but there was no appreciable response (0.28 ng/mL). Magnetic resonance imaging of the pituitary gland demonstrated an ectopic posterior pituitary. Growth hormone replacement was started. Normoglycemia was achieved with diazoxide (15 mg/kg-day) and growth hormone replacement (25 mcg/kg-day).

Genetic screening for *ABCC8*, *GCK*, *GLUD1*, *HADH*, *INS*, *KCNJ11*, *SLC16A1* and *FOXA2* was performed. Sequencing revealed a novel, heterozygous *FOXA2* variant (NM_021784.5 c.304delG [p.A102Rfs*11] [p.Ala102ArgfsTer11]) of likely pathogenicity (ACMG guideline). In the segregation analysis, the same variant was also detected in the proband's father.

CONCLUSIONS

Data regarding FOXA2 mutations is limited and non-endocrine syndromic findings have been reported in previously published cases, but these were absent in the present case. Another feature of this case was a frameshift FOXA2 mutation, which has not been previously reported. While our case emphasizes the importance of comprehensive endocrinological evaluation, it also shows that FOXA2 mutation should be kept in mind, even in cases of hyperinsulinemic hypoglycemia without syndromic findings or dysmorphism.

