TWO NEONATAL DIABETES CASES WITH DIFFERENT MUTATIONS AND TREATMENTS

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BACKGROUND AND AIM

Neonatal diabetes is a monogenic diabetes that can be due to different mutations. Here we report two patients with neonatal diabetes and with two different mutations and treatments.

Case 1

A female infant of consanguineous parents was born at 37 weeks of gestation by normal vaginal delivery with a birth weight of 1900 gr. After birth she was followed in neonatal intensive unit for respiratory distress and hyperglycemia. She didn't have asidosis nor ketosis. She was treated with subcutaneous kritalized insulin. She had 2 healthy siblings and one sibling on growth hormone treatment due to growth hormone bio-inactivity. Her family history was insignificant for diabetes.

At the age of 1 month she was referred because of uncontrolled high blood glucose levels. On admission her body weight was 2330 gr, height was 47 cm, head circumference was 35 cm. Her physical examination was normal except hip dysplasia.

Laboratory tests revealed a venous glucose of 354 mg/dl with glycosuria, but no ketonuria or acidosis. Serum C-peptide level was 0.01 ng/ml (normal range: 0.9-4.3 ng/ml), hemoglobulin A1c was 7.3% (normal range: 4.8-6%) and tests for diabetes autoantibodies (antiGAD, ICA,IA2) were negative. In the complete blood count Hb level was 9.5 mgr/dl, and mean corpuscular volume MCV was 85.1 fL (normal range: 81-99 fL). The blood film showed no signs of megalobastic anemia. Serum folic acid, thiamine and vitamin B12 leves were normal. Serum thyroid hormones were with in normal limits (TSH: 1.75 mIU/L, fT4: 1.06 ng/dl). Kidney and liver function tests were all within normal ranges. The patient was diagnosed as neonatal diabetes and insulin regimen was changed to SC NPH insulin with which blood glucose levels couldn't be stabilized. Thus insulin regimen was changed to detemir insulin, with rapid acting insulin adjustment when needed. But this regimen was not successful in controlling the blood glucose levels. Finally detemir insulin was replaced with glargine insulin that acheived more stable blood glucose levels. She was also significant with diarhea episodes and stool tests revealed malabsorption. Abdominal ultrasonography revealed normal liver and kidneys but pancreas was not visualized. For exocrine pancreas insufficiency enzyme replacement therapy was added to her treatment which she responded well. At her last visit she was 2 years old, her body weight was 11.7 kg (-0.90), height was 83 cm (-1.10), head circumference was 46.5 cm with normal mental and motor development.

DNA sequencing and genetic analysis

A homozygous g.23508363A > G mutation affecting a highly conserved nucleotide within a recently identified distal enhancer *PTF1A*was identified. Functional analysis showed that this mutation disrupts enhancer activity and is likely to result in decreased PTF1A expression during pancreatic development (Weedon et al. 2014 Nat Gen 46:61-64). Her mother and sister had the same mutation heterozygously. Her brother had no mutation. Unfortunately his fathers genetic analysis couldn't be done.

Case 2

A male infant of nonconsanguineous parents was born at 35 weeks of gestation by spontan vaginal delivery with a birth weight of 3400 gr. His seizures as arm movements had started when he was 1 months old which then progressed as tonic clonic convulsions. He was the first and only child of his family and his family history was insignificant for diabetes.

At the age of 3 months he was referred because of high blood glucose levels and failure to thrive. On admission his body weight was 4460 gr (-3.78), height was 62.5 cm (-0.40), head circumference was 40 cm. His physical examination revealed hypotonia and decreased muscle strength in 4 extremities. He was not following with his eyes.

Laboratory tests revealed a venous glucose of 600 mg/dl with glycosuria, but no ketonuria or acidosis. Serum C-peptide level was 0.72ng/ml (normal range: 0.9-4.3 ng/ml), hemoglobulin A1c was 11.4% (normal range: 4.8-6%) and tests for diabetes autoantibodies (antiGAD, ICA, IA2) were negative. In the complete blood count Hb level was 11.4mgr/dl, and mean corpuscular volume MCV was 84 fL (normal range: 81-99 fL). The blood film showed no signs of megalobastic anemia. Serum folic acid, thiamine and vitamin B12 levels were normal. Serum thyroid hormones were with in normal limits (TSH: 1.75 mIU/L, fT4: 1.06 ng/dl). Kidney and liver function tests were all within normal ranges. With our previous experience we started glargine insulin. Humalog insulin was added when needed according to his blood glucose levels. His tonic clonic convulsions continued which was unrelated with his blood sugar levels. An EEG was performed and an antiepileptic was started. Neonatal diabetes, epilepsy, and failure to thrive suggested DEND syndrome. He was heterozygous for a previously reported *KCNJ11* missense mutation, p.C166Y. After the determination of this mutation glibenclamid an oral antidiabetic belonging to sulfanylurea group was started according to the protocol of Hattersley A. (A.T. Hattersley@ex/ac/uk). In the follow up his glibenclamid dose was increased while insulin dose was decreased. With this treatment regimen his blood sugar levels were controlled and although not very significant a relative improvement (normal muscle tone, eye contact) in his neurological status was observed in 7 months of follow-up. At his last visit he was 10 months old, his body weight was 6190 gr (-4.08), height was 74 cm (0.03), head circumference was 42 cm. He was on glibenclamide and insulin treaments at doses of 10 mg/day and 4U/day (2U glargine and 2 U Humalog insulins) respectively. Unfortunately our patient didn't come to follow-up controls till then despite several call ups.

DNA sequencing and genetic analysis

He was heterozygous for a previously reported *KCNJ11* missense mutation, p.C166Y. The p.C166Y mutation has been reported previously in patients with developmental delay, epilepsy and neonatal diabetes (DEND) syndrome (litera). This mutation is predicted to be pathogenic and the result confirmed a diagnosis of neonatal diabetes due to a mutation in the Kir6.2 subunit of the KATP channel (Flanagan et al. 2006 Diabetolgia 49:1190-1197). Unfortunately his parents genetic analysis couldn't be done.

CONCLUSION

Although it can be diagnosed clinically genetic analysis is relevant thus regarding to the mutation, treatment and prognosis can be determined.