Case Report

L225P Mutation of ABCC8 Gene: A Case of Transient Neonatal Diabetes Mellitus with Thrombophilic Predisposition and Epilepsy

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Abstract

Neonatal diabetes mellitus (NDM) is defined as a rare disorder of glucose metabolism in the first six months of life, transient (TNDM) or permanent (PNDM). TNDM usually resolves by 18 months, though it might relapse later in life; PNDM requires lifelong therapy with insulin or/and sulfonylurea. Etiology of NDM is monogenic and genetically heterogeneous. TNDM is often caused by an over-expression of paternal genes on chromosome 6 or by mutation in KCNJ11. Either way the release of insulin is reduced. PNDM is mostly associated with two genes, KCNJ11and ABCC8, which encode, respectively, Kir 6.2 and SUR1, subunits of beta cells K-ATP channel. K-ATP channel is constitutively open, hyperglycemia increases the intracellular ATP levels that cause the closure of K-ATP channel and the depolarization of beta cell causing release of insulin. Inactivating mutations in Kir 6.2 or SUR1, K-ATP channel remains open leading to impaired insulin secretion and neonatal diabetes. Here, we report a case of a three months old baby with diagnosis of NDM and thrombophilic predisposition, referred to emergency pediatric department because of intercurrent ipsilateral clonus to the upper and lower right limbs from a few days, successor seizures during the recovery and incidental finding of hyperglycemia. Child was initially treated with insulin, subsequently was started therapy with glybenclamide for 13 months with progressive decal age. The child was also successfully weaned by treatment with sulfonylureas and epilepsy was well controlled with Phenobarbital.

Keywords: Neonatal diabetes mellitus; ABCC8 mutation; Glybenclamide; Epilepsy

Case Report

A three-months-old baby was referred to emergency pediatric department of Policlinico Umberto I Institute, Rome, because of intercurrent ipsilateral clonus to the upper and lower right limbs, in flexion and internal rotation, slight reduction of the rotation of the head to the right, slight reduction in speed and amplitude of the movements of the upper right limb with closed hand. There was asymmetry of the right emiface, slightly closed eye and reduced motility of mouth.

He was born at 39 gestational weeks after a complicated pregnancy by single umbilical artery and placental senescence diagnosed at 24th week. Birth weight: 2470 g, length: 48 cm and Apgar score: 9 and 10. There was family history for autoimmune diseases and ischemic accidents but none for diabetes and seizures.

On physical examination the infant was awake, well hydrated. Respiratory rate: 34/min, Heart rate 133 bpm, temperature 36.9°C, Blood pressure: 65/45 mmHg.

The first-line findings: Ph: 7.4, HCO3-: 19 mEq/L, pCO$_2$: 41 mmHg, K+: 4.8 mmol/L, BE: 0.6 mmol/L, Na: 135 mmol/L, Cl: 94 mmol/L, Ca: 10.8 mg/dL, Glucose: 413 mg/dL, Lactic acid: 1.9 mmol/L.

Epilepsy was unresponsive to intravenous midazolam (0.1 mg/kg), so he received increasing doses of Phenobarbital and Phenytoin with an effective management of epilepsy.

Hyperglycaemia was initially treated with intravenous saline solution and ultrarapid insulin. After, he received subcutaneous insulin with good glycaemic control.
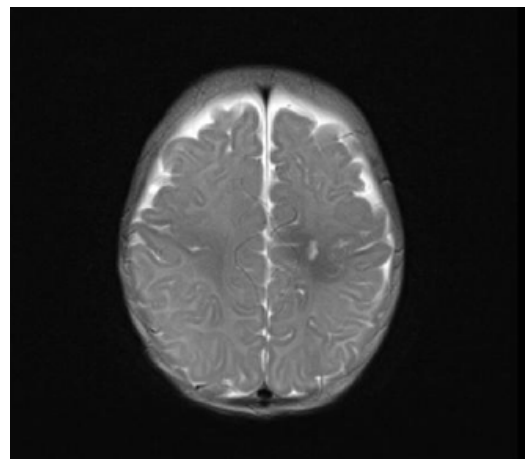
Figure 1: Small area of restricted diffusion in the white matter areas of the corona radiate on the left front seat, referred to an uncertain hypoxic-ischemic acute suffering of parenchyma in acute phase.

EEG showed partial motor epilepticus status with left occipital starting. Blood culture and lumbar puncture were negative. HbA1c: 117 mmol/mol, Apo B1: 1.28 (0.58-1.13), Triglycerides: 297 mg/dl

(37-278), Total Cholesterol: 239 mg/dl (109-204), LDL: 156 mg/dl (35-125), D dimer: 476 ng/ml.

The stool following breastfeeding was normal, showing no pancreatic exocrine deficiency.

Thrombophilia screening showed the following abnormal results: Proteina C: 42 (n. v 70-115), Protein S: 54 (n. v 64-124), Factor II G20210A: heterozygous, MTHFR C677T: heterozygous, INR: 1.01, PTT SEC: 39.19 sec (n.v 26.40-36.80), PTT RATIO: 1.32 (n.v 0.90-1.20).

Brain magnetic resonance imaging (MRI) showed a small area of restricted diffusion in the white matter areas of the corona radiate on the left front seat, referred to an uncertain hypoxic-ischemic acute suffering of parenchyma, disappeared at the following MRI, after six days (Figures 1 and 2).

Molecular biology exam performed on DNA examining KCNJ11 (Kir 6.2), INS and ABCC8 (SUR1) genes. The two exons of the gene INS, exon of the gene KCNJ11 and 39 exons of the ABCC8 gene were amplified by PCR and sequenced by capillary electrophoresis. The sequences are inclusive of intron-exon junctions. It was found the mutation in the heterozygous CTGàGCC in position 674 of the gene ABCC8, with substitution of Leucine 225 in Proline (L225P). This is a de novo mutation.
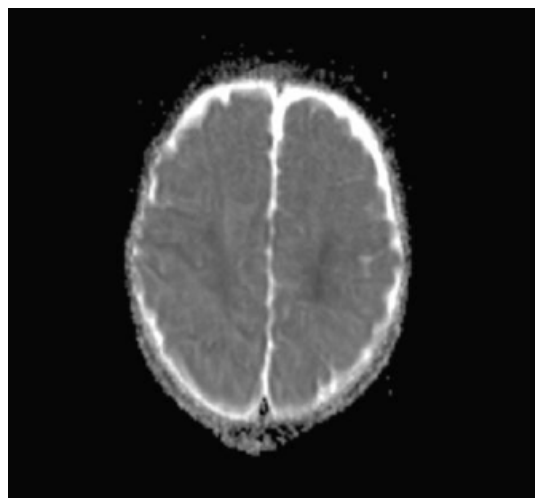
Figure 2: Subacute phase, after six days.

Parents gave their informed consent prior the switching to Glybenclamide. Was administred glargine insulin 6-4 IU and regular one 0.3 -0.4 IU/kg at meals for 17 days. After molecular genetics results we had introduced an oral suspension of insulin secretagogue, Glybenclamide for four weeks:

- 1st week 6 IU Glargine + 0.3 mg/kg/day of Glybenclamide.

- 2nd week 4 IU Glargine + 0.4 mg/kg/day of Glybenclamide.

- 3rd week 3IU Glargine + 0.4 mg/kg/day of Glybenclamide.

- 4th week 2/1 IU Glargine + 0.4 mg/kg/day Glybenclamide.

After 2 months of treatment with Glybenclamide, it was started decal age because of reduced demand from 0.4 mg/kg/day to 0.05 mg/kg/day and after 13 months treatment was ended.

Discussion

The etiology of NDM differs from insulin dependent diabetes mellitus Type 1 (DM1). NDM is monogenic, has not anti-insulin, anti-islet cell and anti-glutamic acid decarboxylase antibodies.

Various syndromes and genetic diseases have been reported in PNDM. Our patient has no signs of any syndromes [1-12].

A subgroup of mutations cause severe clinical profile characterized by delayed development of motor, intellectual and social skills, muscle weakness, epilepsy, facial dimorphisms and Neonatal Diabetes (DEND syndrome) [13-15].

Approximately 20% of cases with mutation in KCNJ11 and ABCC8 have extra pancreatic features, the most severe of which is DEND syndrome. Studies suggest that the severity of the clinical phenotype reflects the extent of the reduction of the channel ATP sensitivity [16].

Thus, patient affected by mutations that produce a larger increase in K-ATP are more likely to develop DEND syndrome [14,15].

Our child did not show any intellectual-cognitive and motor deficits but only a partial motor functional limitation linked to cerebral ischemia, so we have excluded DEND syndrome for differential diagnosis, but we hypothesized that stroke and mutation of the K ATP channels caused seizures in sinergy.

We would like to focus our attention on epilepsy crisis, which were the first clinical sign to manifest without diabetic ketoacidosis neither neurological delay but the result of a series of concomitant factors such as hyperglycemia, familial hypercholesterolemia, MTHFR and prothrombin gene mutation predisposing to thrombotic risk.

EEG was performed on the first day and the following days of hospitalization. It showed an epileptic alteration and he was treated with phenobarbital (15 mg/twice a day). There are many K ATP channels in the brain so, if they are mutated could cause an elongation of depolarization time with alterations of the electrical conduction.

Treatment with Glybenclamide improved glycemic control, as pointed out by HbA1c levels (median HbA1c pre-Glybenclamide 12.9% (117 mmol/mol), post-transition HbA1c 6.3% (45 mmol/mol), without increase of hypoglycemic episodes. Interestingly, the patient enhanced his production of insulin, requiring progressively smaller doses of Glybenclamide until he stopped treatment at 19 months of age. HbA1c after 3 months from the end of therapy was 4.7% (28 mmol/mol). Our patient, even if showing a mutation already described in literature as PNDM [17,18] to date, after 12 months from the end of therapy does not require any treatment for diabetes. Considering the excellent glycemic control and HbA1c values, we made diagnosis of TNDM.

As previously described in literature, the mutation of the gene ABCC8 (L225P), is mostly responsible of PNDM. We affirm that this mutation doesn't always decode the same phenotype. Our patient certainly suffered of TNDM because after 13 months he was also weaned off Glybenclamide and is currently under an optimal glycemic control. However, our patient is the first case of TNDM induced by substitution of L225P in ABCC8 gene reported in literature [19-28].

Acknowledgement

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