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A successful transition to sulfonylurea treatment in male infant with neonatal diabetes caused by the novel abcc8 gene mutation and three years follow-up

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Abstract

Neonatal diabetes mellitus is a rare monogenic disease with incidence of 1/90,000 new-borns. A case of two months aged male infant with life threatening diabetic ketoacidosis is presented with novel ABCC8 gene mutation (p.F577L), successful transition from insulin to sulfonylurea and follow-up of three years.

Keywords

Neonatal diabetes; ABCC8 mutation; Sulfonylurea

1 Introduction

Neonatal diabetes mellitus is a rare monogenic disease with incidence of 1/90,000 newborns [1]. It begins in the first six months of life as a transient (resolves within 12 months of age and reappear in adolescent period) or permanent form. Intrauterine growth restriction, muscle weakness, developmental delay, learning difficulties and epilepsy can be part of clinical presentation [2,3]. In its background is not autoimmune mechanism, but mutations in potassium ATP-sensitive channel (KCNJ11, ABCC8) and INS genes, where successful transitions from insulin to sulfonylurea therapy were described [4–10].

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Conflict of interest
The authors state that they have no conflict of interest.

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2 Case report

At the age of two months, male infant was admitted to the intensive care unit in life threatening diabetic ketoacidosis (blood glucose > 27.8 mmol/l, pH < 6.8, pO_2 11.7 kPa, pCO_2 1.5 kPa, non-measurable standard HCO_3^-, massive glycosuria and ketonuria). The trigger was upper respiratory tract infection started a week ago. Examination revealed soporous and dehydrated child, with reduced subcutaneous fat (BL 54 cm, BW 3400 g) and Candida mucosal infections.

This was the second child from the second controlled pregnancy, completed in term (40 GW) with elective caesarean section, without uterine growth restriction BL 50 cm, BW 2650 g, Apgar score 7/9. During the first month of life he was breast fed and from the second month exclusively on the adapted milk formula with large amounts of water between meals (up to 400 ml/24 h).

Family history was negative for diseases of importance to heredity and the elder child aged 4 years was healthy.

Upon admission, the therapy for ketoacidosis (ISPAD protocol) was initiated. Insulin infusion (0.025–0.05 units/kg/h) was adjusted according to the glycaemic profiles and the patient was gradually converted into a euglycaemic state. 24 h later, oral intake began and treatment continued with s.c. short acting insulin, then intermediate acting insulin plus two-dose administration of short acting insulin on demand (~1.5 units/kg/day).

Additional laboratory analyses revealed glycosylated haemoglobin 7.8% (normal 4–5.9), C peptide 0.2 ng/ml (normal 0.8–3.9), GAD antibody 2.7 IU/ml (normal < 10), anti IA2 10.5 IU/ml (normal < 10), anti ICA 4.3 IU/ml (normal < 4), HLA-DRB1 * 07 * 09/DQB1 * 02 * 03 with normal thyroid hormones and TSH. After 5 weeks the infant was discharged from the hospital on premixed insulin twice daily (1.5 units/kg/d).

Genetic analysis for neonatal diabetes and mutation testing of the KCNJ11, ABCC8 and INS genes has been undertaken as part of research study. Sequence analysis has identified a novel heterozygous missense mutation, p.F577L (p.Phe577-Leu) in patient's exon 12 of ABCC8 gene (DNA Description c.1729T > C), thus confirming diagnosis of neonatal diabetes due to heterozygous mutation in the SUR1 subunit of the pancreatic ATP-sensitive potassium channel *de novo*, since in his parents' leukocyte DNA the mutation was not detected.

The result allowed for the possibility of switching to the preparation of sulfonylureas and at the age of 5.5 months (BL 66 cm, BW 7400 g, the boy was translated to glibenclamide 1.75 mg/day divided in two equal doses, gradually reducing insulin dose. After a morning hypoglycaemia of 2.9 mmol/l, the evening dose was stopped and treatment continued with a single morning dose of 0.875 mg, and afterwards halved to 0.44 mg/day. Repeated morning borderline hypoglycaemia of 3 mmol/l led to further decreasing of glibenclamide to as little as 0.22 mg/day (Table 1) which is the current therapy. Glycosylated haemoglobin remain in normal range and anthropometric parameters were optimal.

3 Discussion

ABCC8 gene provides instructions for building SUR1 protein – subunit of the pancreatic ATP-sensitive potassium channel (sulfonylurea receptor). Closing this channel opens the flood-gate for insulin release. Mutations of ABCC8 gene have been found to cause congenital hyperinsulinism and permanent or transient form of neonatal diabetes. The p.F577L mutation has not been reported in the literature to date. In most patients with K_{ATP} channel mutations, improved glycaemic control may be achieved with sulfonylurea preparation [11–14], thus glibenclamide was successfully introduced (it can also improve symptoms of developmental delay). Clinical course and low levels of C peptide speak in favour of permanent neonatal diabetes in this patient. Each of this patient's offspring will be at 50% risk of inheriting this mutation and developing neonatal diabetes.

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Table 1

Transition of patient with ABCC8 novel mutation (p.F577L) from insulin to sulfonylurea and three-years follow-up.

Age (months)	Treatment	Insulin preprandial (μU/ml)	Insulin postprandial (μU/ml)	C-peptide postprandial (nmol/ml)	C-peptide postprandial (nmol/ml	HbA1c (%)
2	Insulin 1.5 U/day			0.20		7.8
5.5	Decreasing insulin and introducing glibenclamide 1.75 mg/day 0.24 m g/kg/day ↓ 0.875 mg/day 0.12 mg/kg/day	Transition period				5.8
8	Glibenclamide 0.44 mg/day 0.058 mg/kg/day	3.4	7.0	0.40	0.54	5.6
16	Glibenclamide 0.44 mg/day 0.039 mg/kg/day	1.8	4.3	0.23	0.61	5.2
34	Glibenclamide 0.22 mg/day 0.016 mg/kg/day	2.1	5.3	0.34	1.18	5.1