A novel ABCC8 mutation illustrates the variability of the diabetes phenotypes associated with a single mutation

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Abstract

Aim. – ATP-sensitive potassium channels are important regulators of insulin secretion. They consist of four sulphonylurea receptor (encoded by ABCC8) and four inwardly rectifying protein (encoded by KCNJ11) subunits. Activating ABCC8 mutations lead to decreased insulin secretion and to diabetes. Wide phenotype variability is associated with single ABCC8 mutations, ranging from transient or permanent neonatal diabetes (ND) with or without developmental delay (DEND syndrome) to very mild phenotypes. This report describes the case of a Caucasian infant diagnosed with ND at the age of 2 months due to a novel ABCC8 missense mutation.

Methods. – ABCC8 was analyzed by sequence analysis. The mutation was present in the patient and her family and was found to be associated with phenotypes ranging from ND to asymptomatic impaired fasting glucose (IFG).

Results. – A novel His863Tyr ABCC8 mutation was identified in a 2-month-old girl diagnosed with ND. After an initial insulin treatment, treatment with glibenclamide was initiated and the treatment with insulin discontinued. The same mutation was found in her father, who had been fortuitously diagnosed with diabetes and had an HbA1c level of 9% (74.8 mmol/mol). The patient’s brother and mother both had normal fasting glucose, and were not found to be carriers of the mutation. However, the same mutation was found in her grandmother, who had been asymptomatic and discovered IFG (6.9 mmol/L) with an HbA1c of 6.8% (50.8 mmol/mol).

Conclusion. – This case describes a novel ABCC8 mutation and offers a further illustration of the highly variable phenotypes associated with an identical mutation present across three generations.

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Keywords: Neonatal diabetes; SUR1; ABCC8; K_ATP channels

Résumé

Une nouvelle mutation d’ABCC8 illustre la variabilité des phénotypes diabétiques associés à une mutation unique.

Objetif. – Les canaux potassiques sensibles à l’ATP sont d’importants régulateurs de la sécrétion d’insuline. Ils consistent en quatre sous-unités SUR1 (codées par ABCC8) et en quatre sous-unités Kir6.2 (codées par KCNJ11). Les mutations activatrices d’ABCC8 engendrent une diminution de la sécrétion d’insuline et donc un diabète. L’expression d’une mutation ABCC8 donnée est très variable, allant d’un diabète néonatal (DN) à un diabète moins sévère. Nous décrivons le cas d’un patient présentant un DN à l’âge de deux mois, dû à une nouvelle mutation ABCC8.

Méthodes. – ABCC8 a été analysé par séquençage. Nous montrons une mutation chez le patient et sa famille et démontrons qu’une même mutation peut être associée à un phénotype allant d’un DN à une altération asymptomatique de la glycémie à jeun.

Résultats. – Nous décrivons une nouvelle mutation dans ABCC8 chez une fillette de deux mois avec ND. Après une insulinothérapie initiale, un traitement avec du glibenclamide a été instauré, permettant l’arrêt de l’insuline. La même mutation a été trouvée chez le père de la patiente, chez qui un diabète avec HbA1c à 9% (74.8 mmol/mol) a été diagnostiqué. Le frère et la mère avaient une glycémie à jeun normale et n’étaient pas porteurs de la mutation. Finalement, la même mutation a été trouvée chez la grand-mère paternelle qui présentait une hyperglycémie modérée à jeun (6,9 mmol/L) avec une HbA1c à 6,8% (50,8 mmol/mol).

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1. Introduction

ATP-sensitive potassium (K_{ATP}) channels play a key role in the regulation of insulin secretion by pancreatic beta-cells. They couple the metabolic activity of these cells to the electrical activity of their plasma membranes [1], thereby linking the level of blood glucose to secretory activity. Thus, increased metabolic activity due to high blood glucose closes K_{ATP} channels, which induces membrane depolarization and opening of voltage-gated calcium channels, leading to calcium influx into the cytoplasm and insulin exocytosis. Conversely, decreased metabolic activity opens K_{ATP} channels, thereby inhibiting insulin secretion [2]. K_{ATP} channels have an octameric structure comprising four sulphonylurea receptor 1 (SUR1, encoded by ABCC8) and four inwardly rectifying protein (Kir6.2, encoded by KCNJ11) subunits. SUR1 acts as a regulator of the channel, whereas the Kir6.2 subunits act as an ion pore [3–5].

More than 200 mutations have been documented in the ABCC8 gene [8]. Those inactivating the gene lead to excess insulin secretion and, in turn, to neonatal hyperinsulinism and hypoglycaemia [7]. In contrast, activating mutations lead to decreased insulin secretion. Initially, this condition was reported to be associated with transient or permanent neonatal diabetes (ND) [6,9], and was sometimes associated with developmental delay and epilepsy, a condition termed ‘developmental delay, epilepsy and neonatal diabetes’ (DEND) syndrome’ [6]. Since then, several studies have demonstrated milder diabetic phenotypes and wide phenotype variability in association with a single ABCC8 mutation, ranging from DEND syndrome to a very mild phenotype [10].

The present report describes a novel ABCC8 mutation that further illustrates the variable phenotypes that may be associated with a single gene mutation. In this case, a Caucasian infant was diagnosed with ND at the age of 2 months due to a novel ABCC8 His863Tyr mutation. Analysis of the patient’s family revealed diabetes mellitus (DM) in her father and impaired fasting glucose (IFG) in her grandmother, both of whom had been asymptomatic so far.

2. Methods

ABCC8 and KCNJ11 were analyzed in the proband by sequence analysis as previously described [11]. Genetic testing was also offered to the patient’s relatives, and all gave their written informed consent to undergo the tests. In silico predictions of pathogenicity were carried out using the online tools SIFT, PolyPhen-2 and Align-GVGD included in Alamut version 2.0 software (Interactive Biosoftware, Rouen, France).

3. Case report

This 2-month-old girl was born at 39 weeks of gestation with a normal weight of 2795 g and length of 47 cm, from two Caucasian, non-consanguineous parents. She was diagnosed with ND after the discovery of glycosuria when her urine was analyzed in the setting of an unexplained fever, and was referred to our centre for further investigations. Blood gases were normal, blood glucose was 14.3 mmol/L, HbA1c was 10% (normal values: 4–6%; 85.7 mmol/mol, normal values: 20–42 mmol/mol), insulin was < 1 mIU/L (normal values: 1–8.5 mIU/L), C-peptide was 0.1 nmol/L (normal values: 0.2–1 nmol/L), and anti-glutamic acid decarboxylase (GAD), anti-IA2 and anti-islet autoantibodies were all negative. Height and weight were normal for her age. She was initially treated with 0.05 IU/kg/h intravenous insulin. The next day, subcutaneous insulin was started with a pump, initially at 0.9 IU/kg/day. At the age of 3 months, the levels of HbA1c had decreased to 5.6% (37.7 mmol/mol). Subsequently, ABCC8 and KCNJ11 were sequenced, and a novel heterozygous ABCC8 mutation (c.2587C > T, His863Tyr) was identified in exon 22. In silico analysis based on SIFT (score 0.02), PolyPhen-2 (prediction score 0.99) and Align-GVGD (prediction class C25) predicted that this mutation was likely to be pathogenic.

At the age of 12 months, insulin secretion was evaluated by C-peptide measurement during a glucagon test. During this test, C-peptide remained lower than the detection limit of 0.1 μg/L under basal and stimulated conditions, and treatment with glibenclamide was started at an initial oral dose of 1.25 mg three times a day. The initial insulin dose of 0.3 U/kg/day was progressively reduced and the patient was finally weaned off the insulin treatment. Thereafter, glucose homeostasis was satisfactory with 0.25 mg of glibenclamide taken orally twice a day, and HbA1c was between 6 and 7.1% (42–52 mmol/mol). At the age of 19 months, the glucagon test was repeated and showed a basal C-peptide level of 0.54 μg/L, which increased to 0.91 μg/L (normal values: 0.6–3.02 μg/L) upon stimulation. The patient’s subsequent HbA1c levels remained between 6.2% (44.2 mmol/mol) and 6.3% (45.3 mmol/mol).

The rest of the proband’s family was also analyzed (Fig. 1), and the ABCC8 mutation was found in her father, who had been asymptomatic so far; he proved to have elevated fasting glycaemia and an HbA1c of 9% (74.8 mmol/mol), thus permitting the diagnosis of DM [12]. Autoantibodies were negative and treatment with metformin normalized his blood glucose. The patient’s brother and mother had normal fasting blood glucose and were not found to be carriers of the mutation. However, the same mutation was found in her grandmother, who also had
been asymptomatic. Her fasting blood glucose was slightly elevated at 6.9 mmol/L and her HbA1c was 6.8% (50.8 mmol/mol), permitting the diagnosis of IFG. It is also worth noting that the patient’s grandfather was also diagnosed with diabetes with a fasting blood glucose of 7.6 mmol/L and an HbA1c of 6% (42 mmol/mol), but it turned out that he was not a carrier of the proband’s mutation. Presumably, he had developed type 2 DM. Unfortunately, no oral glucose tolerance test was carried out in any member of the family.

4. Discussion

A novel ABCC8 point mutation was found in exon 22 leading to a C > T substitution in position 2587 of the gene. This induced the replacement of a histidine by a tyrosine residue in position 863 of the resulting SUR1 protein. To date, this nucleotide change has not been reported in any genomic databases (dbSNP, built 132; 1000 Genomes Project release 9, September 2011). The His863Tyr mutation affects an amino acid located in the ABC transporter domain of the ABCC8/SUR1 that is highly conserved across species (including rhesus monkeys, mice, dogs, rabbits, elephants, opossums, platypuses, chickens, lizards, stickleback fish, pipid frogs [Xenopus tropicalis] and pufferfish). *In silico* predictions reported that the His863Tyr mutation was likely to be deleterious for protein function. Altogether, these findings were consistent with a pathogenic mutation.

The mutation was transmitted in an autosomal-dominant fashion across three generations, but resulted in diabetic phenotypes ranging from ND with no neurological involvement to IFG. Thus, while the mutation led to ND with an HbA1c of 10% (85.7 mmol/mol) in our 2-month-old proband, it had been asymptomatic in the proband’s father and grandmother, and had not led to diabetic complications at the time of diagnosis. The different HbA1c levels between the father and grandmother indicated the variable effects of the mutation in these two family members, resulting in DM and IFG, respectively. No autoantibodies were detected in either the proband or in these two members of her family.

As previously described [13], the patient was switched from insulin to oral treatment with glibenclamide, which permitted the progressive reduction and eventual stopping of the insulin treatment. A glucagon test performed after the initiation of glibenclamide showed improved secretion of C-peptide. This illustrates the important clinical implications of identification of the ABCC8 mutation in terms of treatment strategies and patient’s quality of life.

In conclusion, this case report describes a novel mutation of the ABCC8 gene and adds a new description of the highly variable possible phenotypes that may be associated with an identical mutation of the gene, ranging from asymptomatic IFG to ND [14]. Previous reports have so far identified three situations resulting from ABCC8 mutations. The first concerns families where ND is associated with mild phenotypes in adulthood [9,13]. The fact that the same ABCC8 mutation can lead to both a severe phenotype with neonatal onset as well as a much milder phenotype with late onset suggests that other factors, such as the environment (e.g. intrauterine hyperglycaemia) or factors linked to a genetic background of susceptibility at the ABCC8 locus or affecting other loci, could be implicated in the variable clinical expression. The second situation concerns families where all carriers of the ABCC8 gene mutations present with mild phenotypes, but possibly with a tendency to progress from hyperglycaemia to overt diabetes with age, but without ND [10]. Finally, a particular ABCC8 mutation inducing a small change in channel ATP sensitivity has been associated to type 2 DM and impaired glucose tolerance [15].

Thus, given these variable phenotypes, it is mandatory to measure HbA1c and fasting glucose levels in close relatives of a patient, even when they are asymptomatic.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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