Mutations in the ABCC8 gene can cause autoantibody-negative insulin-dependent diabetes

A. Hartemann-Heurtier \( ^a,^\text{*b} \), A. Simon \( ^c \), C. Bellanné-Chantelot \( ^d \), R. Reynaud \( ^e \), H. Cavé \( ^f \), M. Polak \( ^c,^\text{g,h} \), M. Vaxillaire \( ^i \), A. Grimaldi \( ^a,b \)

\( ^a \) Endocrinology, Nutrition and Diabetes Department, Pitié-Salpêtrière Hospital, Assistance publique–Hôpitaux de Paris (AP–HP), 83, boulevard de l’Hôpital, 75651 Paris cedex 13, France
\( ^b \) Faculty of Medicine, University Pierre-et-Marie-Curie Paris-VI, Paris, France
\( ^c \) Pediatric Endocrinology Department, Necker–Enfants-Malades Hospital, Assistance publique–Hôpitaux de Paris (AP–HP), Paris, France
\( ^d \) Genetics Department, Pitié-Salpêtrière Hospital, Assistance publique–Hôpitaux de Paris (AP–HP), Paris, France
\( ^e \) Pediatric Endocrinology Department, hôpital Timone–Enfants, Assistance publique–Hôpitaux de Marseille (AP–HM), Marseille, France
\( ^f \) Genetic Biochemistry Department, Robert-Debré Hospital, Assistance Publique-Hôpitaux de Paris (AP–HP), Paris, France
\( ^g \) Faculty of Medicine, University René-Descartes Paris-V, Paris, France
\( ^h \) Inserm U845, Paris, France
\( ^i \) UMR8090, Centre national de la recherche scientifique, Institute of Biology, Pasteur Institute, Lille, France

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Abstract

Activating mutations in genes \( \text{KCNJ11} \) and \( \text{ABCC8} \), which form the ATP-sensitive \( K^+ \) channel (\( K_{\text{ATP}} \) channel), have been shown to cause transient or permanent neonatal diabetes. We describe here a rather different phenotype: two cases of adult diabetic patients—considered and treated as insulin-dependent diabetic patients since adolescence—who, in fact, turned out to be heterozygous for an \( \text{ABCC8} \) mutation and able to successfully discontinue insulin while taking sulphonylurea treatment.

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Résumé

Des mutations du gène \( \text{ABCC8} \) peuvent être à l’origine d’un diabète insulinodépendant non auto-immun.

Des mutations des gènes \( \text{KCNJ11} \) et \( \text{ABCC8} \) impliqués dans le fonctionnement du canal \( K_{\text{ATP}} \) sont à l’origine de diabète néonataux transitoires ou permanents. Nous décrivons ici un phénotype différent: deux cas d’adultes diabétiques considérés comme des diabétiques insulinodépendants depuis leur adolescence, qui se sont révélés être finalement porteurs d’une mutation \( \text{ABCC8} \), et qui ont pu être transférés sous sulfa-mides hypoglycémiants avec succès.

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Mots clés : \( \text{ABCC8} \) mutation ; Diabète insulinodépendant ; Sulfa-mides hypoglycémiants

1. Introduction

The ATP-sensitive \( K^+ \) channel (\( K_{\text{ATP}} \) channel) in pancreatic \( \beta \)-cells comprises four pore-forming (\( \text{Kir6.2} \)) and four regulatory (sulphonylurea receptor 1; \( \text{SUR1} \)) subunits, which are encoded by the \( \text{KCNJ11} \) and \( \text{ABCC8} \) genes, respectively. Cellular \( K_{\text{ATP}} \) binds to \( \text{Kir6.2} \) to close the potassium channel, whereas increased cellular ADP acts on \( \text{SUR1} \) to open the channel. Activating mutations in these channels reduce sensitivity to the
inhibitory actions of ATP while increasing sensitivity to the stimulatory actions of ADP. This causes the K_{ATP} channel to remain open, even in the presence of glucose, thereby preventing insulin release. Activating mutations in these genes have been shown to cause transient or permanent neonatal diabetes [1,2]. Mutations in the KCNJ11 gene are thought to account for 25 to 50% of all cases of neonatal diabetes [1–3], whereas mutations in the ABCC8 gene are thought to account for 10% of all such cases [4] and frequently cause transient neonatal diabetes [4–6]. Apart from neonatal diabetes, looking for the presence of such mutations is not a routine practice, although these mutations may be responsible for permanent diabetes in both children and adults [4,5]. We describe here two cases of adult diabetic patients, considered and treated as insulin-dependent diabetic patients since adolescence, both of whom turned out to be heterozygous for an ABCC8 mutation.

2. Patient 1

This patient is a male 37-year-old Caucasian with diabetes that was diagnosed by polyuria and polydipsia symptoms when he was 15 years old (in 1983). His body mass index (BMI) was 21 kg/m² at that time, but islet cell autoantibody (ICA) values were then not commonly available. He started with several daily insulin injections. Over the past 10 years, his mean daily insulin dose has been 0.3 IU/kg per day, with a mean HbA1c level of 6.7% (normal: 4–5.6%). In 1999, no ICA were detectable and, in 2006, he still had no chronic diabetes complications.

Patient 1’s mother had diabetes that was diagnosed at the age of 20 years (in 1965) also because of polyuria/polydipsia symptoms. Her BMI was then 24 kg/m². Her treatment consisted of several daily insulin injections, with a mean dose of 0.9 IU/kg per day, and with a mean HbA1c of 8.5%. She had mild diabetic retinopathy, and was suspected of being a mature-onset diabetes of the young (MODY) patient because of her family phenotype (she has numerous orally treated type 2 diabetics in her family), but mutations of the HNF1A and GCK genes were excluded by sequencing. However, her nephew had a son who developed neonatal diabetes in May 2008. At that time, the patient told us for the first time that her own son had had transient neonatal diabetes in 1968 (and is currently being treated with antidiabetic drugs).

4. Investigations and treatment

Ever since the ABCC8 and KCNJ11 gene mutations were discovered, all patients in the French Network for the Study of Neonatal Diabetes Mellitus have been screened. Patient 1’s son was found to have the heterozygous mutation c.1303T > C (p.Cys435Arg) of ABCC8 [4]. Patient 1 himself was also screened and found to be heterozygous for the same mutation. He was hospitalized and received oral glyburide, and was able to discontinue insulin on a 10-mg per day dose regimen. His ICA were negative, and his mean HbA1c over the past 2 years has been 5.8%.

As the son of patient 2’s nephew developed neonatal diabetes, patient 2 herself was also screened and found to have the heterozygous mutation c.4139G > A (p.Arg1380His) of ABCC8. She was hospitalized and received oral glyburide, and successfully discontinued insulin with a regimen of 15 mg per day. Her last HbA1c was 7.3%. Anti-GAD, anti-IA2 and ICA tests were all negative. Her nephew was found to have the same mutation.
Glyburide treatment significantly increased C-peptide release in both patients 1 and 2 (Table 1).

5. Conclusion

This case report shows that a mutation in the ABCC8 gene can give rise to a clinical phenotype of insulin-dependent diabetes with a normal weight, an early age at onset and hyperglycaemia symptoms. A proband with this pattern of transient neonatal diabetes and permanent diabetes diagnosed in adulthood has been reported in several families with mutations of the KCNJ11 and ABCC8 genes [4,5]. In a study where all the parents of probands with neonatal diabetes and mutated ABCC8 were explored, it was concluded that ABCC8 mutations could give rise to a monogenic form of type 2 diabetes with variable expression and age at onset [4,6].

The two cases described here suggest that ABCC8 mutations may also have an autoantibody-negative insulin-dependent diabetic clinical expression. One hypothesis is that K$_{ATP}$-channel mutations may have a biphasic course and that patients diagnosed later in life may have had a period of hyperglycaemia that was undetected in the neonatal period [7]. On the other hand, mutations in the ABCC8 gene can be associated with neonatal hyperinsulinism associated with a severe hypoglycaemia that may progress, within 10 or more years, to insulinopenic diabetes [8,9]. However, clinical hypoglycaemia was not observed during infancy in either of our cases.

Serum markers of islet cell autoimmunity are usually present in typical type 1 diabetes. However, when diabetes onset is more than 25 years earlier, these markers may be missed. In addition, some individuals with insulin-dependent diabetes fail to present with immunological markers at the time of diagnosis. The present report suggests that some of those individuals could have a K$_{ATP}$-channel mutation.

At present, it is impossible to determine the prevalence of these mutations in non-neonatal, non-autoimmune, insulin-dependent-like diabetic patients. The phenotype is non-specific and, in the absence of transient neonatal diabetes in the family, K$_{ATP}$-channel mutation is not usually suspected. Nevertheless, such misdiagnoses can be dramatic in terms of quality of life and risk of diabetic complications, as it appears that sulphonylurea treatment allows discontinuation of insulin injections, and that better glycaemic control is usually obtained with sulphonylurea than insulin in these patients [10].

Conflicts of interest

No conflicts of interest are declared by any of the authors.

References