Endocrinol Diabetes Nutr. 2020;67(10):682–685

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

SCIENTIFIC LETTER

# Effectiveness of sulfonylurea treatment in a patient with a mutation in *ABCC8* (MODY12)☆

## Efectividad del tratamiento con sulfonilureas en paciente con mutación en el gen *ABCC8* (MODY12)

Monogenic diabetes (DM) with beta-cell dysfunction β (MDBD), grouped under the term MODY *(maturity-onset diabetes of the young)*, comprises a heterogeneous group of diseases associated with genetic mutations that lead to pancreatic β cell dysfunction.

The diagnostic criteria for MDBD include hyperglycemia, usually before 25 years of age; autosomal dominant inheritance with transmission in at least three generations; similar disease phenotypes among family members; and C-peptide levels maintained within reference ranges for years.

The MODY subtypes differ among each other in terms of prevalence, clinical manifestations and therapeutic requirements.

The prevalence of MODY is not known, though it is estimated that approximately 1-2% of all cases of diabetes could be classified as MODY. The most commonly mutated genes are hepatocyte nuclear factor 1α (HNF1A) and glucokinase (GCK), which cause MODY3 and MODY2, respectively - representing up to 90% of all cases of MODY[1].

We describe a case of MODY12, caused by a mutation in the *ABCC8* gene.

The *ABCC8 (ATP-Binding Cassette subfamily C member 8)* gene, located on chromosome 11, encodes the expression of ATP-sensitive potassium channels (KATP channels) of sulfonylurea receptor 1 (SUR 1) in the pancreatic β cells. Closure of the ATP-sensitive potassium channels is known to be necessary for insulin secretion from glucose-stimulated β cells, while the opening of these channels inhibits insulin secretion.

Gain-of-function mutations in *ABCC8* in humans are associated to MODY, type 2 diabetes mellitus (DM) and gestational diabetes. Some *ABCC8* mutations cause hyperinsulinemia in neonates, while others have been found in cases of neonatal diabetes[2,3].

The patient was a 35-year-old woman from Mexico, living in Spain for about 8 years, and a student of Business Administration and Management. She was a former smoker, with no other toxic habits. No surgical history.

The patient was diagnosed with type 1 DM at 28 years of age in Guadalajara (Spain), where insulin therapy was started and was discontinued after four years due to problems with her residence permit. Subsequently, 10 months before reporting to our clinic, insulin therapy was restarted with a basal-bolus regimen (glargine 37 IU at 08:00 h and glulisine 8 IU with breakfast, 12 IU with lunch, and 6 IU with dinner). During insulin treatment, she reported frequent hypoglycemia episodes (levels as low as 26 mg/dl, capillary blood measurement), which sometimes proved asymptomatic. As microangiopathic complications, she presented moderate non-proliferative diabetic retinopathy. There have been no known macroangiopathic complications to date.

Her medical history moreover included arterial hypertension treated with an angiotensin II antagonist (irbesartan 75 mg) and hypercholesterolemia treated with a statin (atorvastatin 20 mg).

With regard to the family history, her father had suffered diabetes and died in a traffic accident. In addition, she had three siblings with diabetes who died of the disease (she was unable to specify the immediate cause of death). Her mother had no known diabetes, and died at 54 years of age due to acute myocardial infarction. The patient was the youngest of 8 siblings: the three older siblings died of diabetic nephropathy at around 50 years of age; her middle sister, also diabetic, has two daughters diagnosed with type 1 DM (aged 20 and 23 years). All are living in Mexico. The patient has no children, and has had no pregnancies.

She was referred from primary care to our endocrinology outpatient clinic. In view of the high familial burden, a study of monogenic diabetes was requested, resulting in the identification of a pathogenic variant in heterozygosis in exon 13 of the *ABCC8* gene, consisting of a change from guanine in position 1819 to adenine (c.1819 G > A), which implies substitution in the protein of valine 607 protein for methionine (p.Val607Met).

Given these findings, scheduled hospital admission was decided for the start of treatment with sulfonylureas.

During admission, basal insulin was discontinued, treatment was started with gliclazide 60 mg[4] with breakfast, lunch and dinner, and the use of rapid insulin was gradually reduced, maintaining only a bolus of insulin glulisine 6 IU at discharge, with good blood glucose control. The $HbA_{1c}$ concentration decreased from 8.3% to 7.2%, and the C-peptide levels improved: basal upon admission 0.52 ng/ml; post-breakfast upon admission 2.53 ng/ml; basal after start-

☆ Please cite this article as: Lanes Iglesias S, Ares Blanco J, Bellido Castañeda V, Sánchez-Ragnarsson C, Menéndez-Torre E. Efectividad del tratamiento con sulfonilureas en paciente con mutación en el gen *ABCC8* (MODY12). Endocrinol Diabetes Nutr. 2020;67:682–683.

ing sulfonylureas 2.86 ng/ml; post-breakfast after starting sulfonylureas (2 days after start) 4.97 ng/dl.

Two months after hospital discharge, the patient was evaluated in the endocrinology outpatient clinic. The patient reported home capillary blood glucose controls with basal values of 110-162 mg/dl; pre-lunch 86-112 mg/dl; post-lunch 132-213 mg/dl; and pre-dinner 95-161 mg/dl. We decided a gliclazide dose increase to 60 mg with breakfast and lunch, and 90 mg with dinner, and insulin was suspended entirely.

The present case illustrates the clinical characteristics associated to the mutation in the *ABCC8* gene encoding SUR1 (MODY subtype 12). The disease was initially erroneously classified as type 1 DM despite negative pancreatic autoimmune test results.

Consideration of the case as corresponding to MODY was supported by the fact that, after diagnosis, the patient remained without insulin treatment for about three years, with no severe acute complications such as ketoacidosis, and also by the presence in her family of diabetes in at least three consecutive generations.

The genetic study revealed a heterozygous mutation in exon 13 of the *ABCC8* gene. Identification of the MODY subtype is crucial for establishing appropriate treatment. In our patient, diagnostic confirmation allowed the discontinuation of insulin therapy, and thanks to the introduction of sulfonylureas, she improved her metabolic control with no hypoglycemia episodes, increased C-peptide, and decreased glycosylated hemoglobin levels.

Treatment with sulfonylureas in diabetes related to mutations in the *ABCC8* gene is clearly beneficial for both patient quality of life and blood glucose control. A personalized diagnosis of non-classical forms of diabetes is essential for adequate management.

## Acknowledgments

We thank the patient for placing her trust in us and for allowing us to make our experience with her case known.

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# A remarkable cause of endocrine hypertension☆

## Una causa singular de hipertensión endocrina

The detection of an adrenal gland neoplasm in the study of arterial hypertension (AHT) opens up a wide range of diagnostic possibilities, potentially as a cause of or independent from AHT itself. We report a case with this association, with a peculiar diagnostic trajectory and an exceptional final diagnosis.

A 29-year-old woman was referred to the nephrology clinic after the detection of AHT due to headaches starting one year ago. She had undergone surgery at 5 years of age due to left pyeloureteral stenosis, and reported recent pollakiuria with nocturia. She provided a primary care report with mean daytime and nocturnal blood pressure (BP) values of 154/100 and 140/90 mmHg, respectively. The laboratory tests requested by her primary care physician revealed low serum potassium levels in two determinations (3.49 and 3.12 mEq/l), with normal renal function. The expanded study in the Nephrology Department revealed low plasma renin activity (0.2 ng/ml/h) with normal-low aldosterone levels (7.3 ng/dl), normal urinary catecholamines and a CT angiographic scan evidencing a hypervascular right adrenal mass measuring 6 cm in diameter (Fig. 1). After consulting the Endocrinology Department, the study was further expanded with fractionated urinary metanephrines, urinary 3-methoxytyramine and urinary free cortisol – all of them yielding normal values – in addition to ACTH (34.5 pg/ml) and plasma dehydroepiandrosterone (DHEA) (1.31 μg/ml), as well as serum chromogranin A and testosterone – all of which proved normal. Upon assessment in the clinic with these results, the patient presented no menstrual disorders or hirsutism, denied regular intake of liquorice, and had a normal phenotype. Preferential surgery was indicated in view of the size of the tumor, and the serum samples stored in the hospital serum repository were used for simultaneous measurement of intermediate metabolites of steroidogene-

☆ Please cite this article as: Paja-Fano M, Martínez-Martínez A-L, Monzón-Mendiolea A, Espiga-Alzola J. Una causa singular de hipertensión endocrina. Endocrinol Diabetes Nutr. 2020;67:683–685.