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Case Report

Report of a Novel Mutation of ABCC8 Gene Related to MODY12 Phenotype

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Received: September 21, 2022; **Published:** October 14, 2022

Abstract

Monogenic diabetes mellitus encompassed a variety of diabetes. The most common types of which are Maturity- onset diabetes of the young (MODY). ABCC8 gene is one of the genes playing an important role in the function of K-ATP channels and its mutation causes a wide range of diabetes with different manifestations. Different symptoms have challenged the diagnosis, which has directly impacted on the management of patients. Therefore, definitive diagnosis is one of the requirements of medical management of these patients and genetic testing is the best choice. As a result, determining the type of mutation will play a special role in patient's cares and their quality of life.

Keywords: *Mutations; Monogenic Diabetes Mellitus; ABCC8; Diverse Phenotypes; MODY12*

Introduction

In general, monogenic diabetes mellitus is a form of diabetes which mutations are associated with the regulation of insulin levels [1,2]. Maturity-onset diabetes of the young (MODY) is a heterogeneous and mild familial form of monogenic diabetes mellitus with autosomal dominant inheritance that characterized by defects in beta cells function [3]. Among all types of monogenic diabetes, MODYs are the most common form. Four genes, including HNF1B, HNF1A, HNF4A and GCK, account for over 95% of MODY cases in Caucasians, but other mutations of monogenic diabetes include rare types of MODYs [4-6].

Among the 41 genes causing monogenic diabetes, mutations of the two genes encompassed KCNJ11 (Potassium inwardly rectifying channel, subfamily J, member 11) and ABCC8 (ATP-binding cassette transporter, sub-family C, member 8) account for about 40% of cases. They are related to neonatal diabetes. Mutations involving the K-ATP channels often take the form of gain of function rather than loss of function. In the gain of function form, insulin is not released due to the non-closure of the K-ATP channels, and in the loss of function one,

there is a disorder in production and function of the K-ATP channels, called congenital hyperinsulinemia (CHI), which is associated with neonatal hypoglycemia [7,8].

The sulfonylurea receptor 1 (SUR1) is a channel subunit (K-ATP) encoded by the ABCC8 gene [9] and the heterozygous activating form causes MODY 12, which clinical presentations are similar to MODY1 and MODY3 [10]. Genetic testing is pivotal in MODY patient's cares because the type of cares varies from the range of without the need for medication in MODY2 to the need for high-dose sulfonylurea in MODY13 and low-dose in MODY1 and 3 [11,12]. Here we discuss the clinical features, ABBC8 mutation, and related findings in a 2.5-year-old boy.

Case Presentation

A 2.5-year-old boy (currently an 8-year-old boy) referred to the clinic with complaint of polydipsia, polyuria, polyphagia and weight loss that was not associated with ketoacidosis. He was the first child of the family and had no siblings. The patient was born at gestational age of 37 weeks by cesarean section. The weight and height at birth were 2400g and 48 cm, respectively. There was no history of hospitalization, illness, or medication, but he complained of a chronic wound in his right thumb. The patient also mentioned a history of hypoglycemia following an electrical shock. Among the patient's relatives, a history of gestational diabetes mellitus (GDM) was seen in his mother, also his father's uncle, grandmother; mother's aunt had history of diabetes mellitus. No history of autoimmune disease and dyslipidemia was reported. There was no report of developmental delay in his history. There was no history of neonatal hyperinsulinism and hypoglycemia in his first-degree relatives.

Cardiovascular examination was normal and no abnormality was found. The patient's liver biochemical tests were normal. Renal examination showed blood urea nitrogen (BUN) of 12 mg/dl and creatinine of 0.5 mg/dl. In urinalysis (U/A), urine specific gravity (U/SG) was 1015 and no evidence of microalbuminuria and glycosuria was reported. Plasma PH was normal and ketones were not observed in the plasma and urine. In fundoscopy, the vessels of the fundus area were intact, and sign of exudate or bleeding was not observed (5 years after diagnosis). But tooth decay was reported on his dental examination. His physical activity was routine and included walking and swimming.

Evaluation of blood sugar profile included fasting blood sugar (FBS) of 152 mg/dl (NL range, 70 - 126 mg/dl) and HbA1c of 8% (NL range, < 5.7%) as well as lipid profile evaluation such as total cholesterol (TC) of 130 mg/dl (NL range, < 200 mg/dl), low-density lipoprotein (LDL) of 56 mg/dl (NL range, < 130 mg/dl), high density lipoprotein (HDL) of 45 mg/dl (NL range, 35 - 70 mg/dl) and triglyceride (TG) of 100 mg/dl (NL range, < 150 mg/dl). Islet cells analysis was performed for rule out of type 1 diabetes, which included insulin of 8, c-peptide of 0.5, as well as autoantibody profiles such as anti-tyrosine phosphatase ICA 512 (IA2) of 0.1 (> 57.5 IU/mL), islet-cell antibodies (ICA) of 0.2 (≥ 1 IU/mL), anti-insulin autoantibodies (IAA) of 0.2 (> 125 nU/mL) and anti-glutamic acid decarboxylase (GAD) 1 (≥ 5 IU/mL) were negative. No abnormal finding was observed on physical examination.

Initially, the patient's blood sugar (BS) was controlled with 5 units of NPH, due to raising his BS to 272, NPH increased to 10 units in the morning. After a while, BS was 187 and under controlled. Thereafter, due to fluctuating of BS, insulin regimen changed to 15 units of Novo rapid and 15 units of Lantus. He did not experience an episode of hypoglycemia with this regimen.

Due to no evidence of obesity and acanthosis nigricans, normal body mass index (BMI, 17.85 kg/m^2), normal c-peptide, normal insulin, and impaired fasting glucose test (IFGT) MODY was ruled out. Genetic testing by Whole-exome sequencing considered for the patient to evaluate MODYs subtypes included 1 to 14. Genetic analysis revealed a mutation of ABCC8 gene with A to T transition at nucleotide 368 (exon 3). To our knowledge, the replacement of cysteine with tyrosine has been previously reported, but the replacement of phenylalanine with tyrosine is novel. At present, his BS is favorable and his growth is normal.

Discussion

Definite approval of MODY is costly and difficult, but it is relatively easier to manage in terms of treatment and subsequent consultations [13,14]. Referred to CH Lachanse, its prevalence is estimated about 1to 2% of diabetic patients, but accurate statistics of the disease prevalence is not available [15]. The inclusion criteria for MODY diagnosis are based on the family history of disease, clinical manifestations, and laboratory findings because beta cell mutation causes a wide range of disorders. Searching for family history in these patients indicates a disease with autosomal dominant behavior that is inherited at least in 3 consecutive generations with in common phenotypes. The dysfunction of beta cell is accompanied by hyperglycemia, which manifests before the age of 25 and normal range of c-peptide for several years [15-18].

In a study of 1020 neonates whose diabetes was diagnosed before the age of 6 months, genetic analysis was performed on conventional genes involved in the secretion and function of beta cells. 82% of the mutations were reported in common genes that K-ATP channels genes including KCNJ11 and ABCC8 were the most common cases of neonatal diabetes, and the insulin (INS) gene accounted for 10% of all cases [19]. K-ATP channels mutations create a type of neonatal diabetes called transient neonatal diabetes that can recur at older ages. In this classification, KCNJ11 and ABCC8 mutations are the second cause of this type of diabetes [19,20]. Patients with this type of diabetes develop hyperglycemia at 13 to 18 weeks [19-21]. In fact, KCNJ11 and ABCC8 mutations involve the internal and external subunits of the K-ATP channel, respectively, causing these channels remain open. Thus, insulin secretion is not in proportional to the resulting hyperglycemia [19,20] permanent neonatal diabetes mellitus (PNDM) is another category includes half of neonatal diabetes mellitus (NDM) cases that heterozygous mutations of K-ATP channels are account for the most common mutations of PNDM [20,22].

ABCC8 gene can cause a variety of beta cell dysfunction, including MODY, newborn hyperinsulinism, gestational diabetes, and type 2 diabetes. This gene is located on the chromosome 11 and mutations of this gene are associated with an amino acid substitution of the SUR1 (ATP-sensitive K) channels protein impairing insulin secretion [23,24]. There has also been reported an ABCC8 mutation in the form of MODY2 phenotype that was accompanied by mild hyperglycemia without pharmacological intervention [25]. On the other hand, a mutation of ABCC8 gene has been reported in the form of heterogeneous diabetes in a family, which was a gain of function [26]. Genetic analysis in our patient indicated a heterozygous mutation of A.368T, located on chromosome 3, in the form of missense mutation with the substitution of the amino acid tyrosine with phenylalanine. It has not been reported according to the ClinVar and Human Gene Mutation Database (HGMD®). MODY 1, 3, and 12 have similar clinical findings included lack of pancreatic auto-antibodies, lack of obesity, and disease emergence at different ages, childhood and young adulthood [17].

The first case of MODY12 with ABCC8 mutation was reported by Bowman., *et al*. in 2012 which clinical reports of the patient were diversely. The patient had a high BMI (overweight) but no sign of hyperlipidemia was observed in the patient's tests [10,27]. The discordancy between genotype and phenotype of patients with ABCC8 mutations has not been determined precisely, but it can be related to the type of mutations, whether it is a gain of function or loss of function [4,28]. Also factors like genetic modifiers, environmental etiologies, and mutations location have role in developing to this discrepancy [26,28,29]. With all of these interpretations, patients respond well to discontinuation of insulin therapy and continuation with sulfonylurea in infancy or adulthood [4,28].

Diabetic ketoacidosis is a casual finding of diabetic patients, and the prevalence of which increases with age. In addition to the age factor, it's incidence is much higher in a series of neonatal diabetes. In a study, the rate of ketoacidosis was reported 78.8% and 30% of patients with K-ATP channels and INS mutations, respectively. Also, the odds ratio (OR) for ketoacidosis was calculated 1.23 per month with increasing age [30]. Our patient presented with osmotic presentations encompassed polydipsia and polyuria and did not experience ketoacidosis. No findings of obesity and hyperlipidemia were reported in his examinations. He had a strong family history of diabetes and it was mentioned in his past medical history (PMH) that he experienced a major stress by electrical shock. Sulfonylureas are generally considered to be the usual treatment for patients with ABCC8 mutation [28,31].

Insulin is also used as a treatment in these patients. Therefore, it is necessary to choose the appropriate treatment between insulin and sulfonylureas because it is a determining factor in the patient's metabolic profile [32]. In our patient, the treatment initiated with 5 units of NPH, but after a few months, the patient's BS was out of control and some periods of hyperglycemia were reported. Then, the dose of NPH increased to 10 units, which responded within a few months. Months later, the patient came back with reports of BS fluctuations, sometimes with normal BS and sometimes with high BS. So, we had to change the patient's regimen with Novo rapid plus Lantus. The BS is currently controlled by 15 units of Novo rapid and 15 units of Lantus. He had not experienced conditions like hypoglycemia and hyperglycemia anymore. the patient's HbA1c level decreased about 3.5% (from 10.2 to 6.5).

Therefore, determining the type of MODY is important in terms of therapeutic management, lifestyle, and complications like hypoglycemia and gain of weight. These issues raise the importance of genetic analysis more and more in MODY cases because in these patients, especially MODY12, insulin response to glucose is a significant factor in determining the metabolic profile of these patients [28]. It should be noted that an important factor in BS fluctuations in ABCC8 mutations is insulin administration, which can be a risk factor for progression to diabetic vascular complications. Comparison of glucose sensors during treatment with insulin and sulfonylurea in patients indicated that during treatment with sulfonylurea, the target time for BS significantly increased and caused a decreased in vascular complications [33]. In our patient, BS fluctuations were probably owing to insulin administration, but the patient's BS was under control for several months.

Conclusion

We discussed a single nucleotide mutation in a MODY12 case that showed the replacement of the amino acid phenylalanine with tyrosine in nucleotide # 368, which has not been reported recently. Although the criterion for Mody patients is helpful in diagnosing patients, it cannot replace genetic testing due to variations in mutations and clinical manifestations. The type of treatment chosen will directly affect the response of plasma glucose levels by beta cells, complications including hyperglycemia, obesity, vascular complications and patients' quality of life. Choosing the right and timely treatment can achieve us to therapeutic goals sooner, such as optimal BS control and reducing the risk of vascular complications.

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Volume 11 Issue 11 November 2022
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