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BLK-1 Mutation with Maturity Onset Diabetes of the Young 11: A Case Report

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Abstract

MODY (Maturity Onset Diabetes of the Young) is a kind of diabetes that has an autosomal dominant inheritance pattern and is caused by monogenic abnormalities in cell activities. MODY is the most common form of monogenic diabetes in Europe, accounting for 1% to 2% of all diabetes cases. Some of the molecular pathways that cause MODY have been clarified in recent years improved genetic approaches. MODY is caused by at least fourteen separate genes, and various mutations have been discovered. Mutations in the B Lymphocyte Tyrosine Kinase (BLK) locus are in the very rare group. It is an important point that the number of cases with this MODY type, which is defined as BLK 1 mutation, in other words MODY 11, is low and it has not been reported in childhood. Here, we present a case who presented with hyperglycemia and found a BLK-1 mutation in the follow-up.

Keywords: Diabetes; MODY; Insulin therapy

Background

MODY (Maturity Onset Diabetes of the Young) is a kind of diabetes that has an autosomal dominant inheritance pattern and is caused by monogenic abnormalities in cell activities [1]. MODY is the most common form of monogenic diabetes in Europe, accounting for 1% to 2% of all diabetes cases [1-5]. Tattersall and Fajans proposed in 1975 as clinical criteria for the diagnosis of MODY, who were diagnosed with diabetes before the age of 25 and had diabetes in at least two or ideally three generation [6]. Some of the molecular pathways that cause MODY have been clarified in recent years improved genetic approaches. MODY is caused by at least fourteen separate genes, and various mutations have been discovered [7]. MODY, like many other genetic diseases, is inherited in an autosomal dominant pattern and refers to a collection of disorders with a wide range of genetic, metabolic, and clinical features [8]. MODY has been divided into 14 subtypes, each with its own set of symptoms in terms of gene mutation, onset age, therapy, and hyperglycemia pattern [9]. Mutations in the genes 'Hepatocyte Nuclear Factor 4 Alpha (HNF4A), Glucokinase (GCK), and Hepatocyte Nuclear Factor 1 Alpha (HNF1A) cause the most common types [3]. Borowiec discovered that B Lymphocyte Kinase (BLK) is a previously unknown modulator of insulin production and secretion that increases the expression of critical cell transcription factors PDX-1 and NKX6.1 [10]. Although case reports of many types of MODY have been published in recent years, this type of diabetes is still rare and much information about the phenotypic characteristics and pharmaceutical approach is unknown.

Mutations in the B Lymphocyte Tyrosine Kinase (BLK) locus are in the very rare group. It is an important point that the number of cases with this MODY type, which is defined as BLK 1 mutation, in other words MODY 11, is low and it has not been reported in childhood. Here, we present a case who presented with hyperglycemia and found a BLK-1 mutation in the follow-up.

Case Presentation

We present a 17-year-old patient who presented with complaints of polyuria, polydipsia and weight loss in the last two months. It was learned that the patient was born 3,600 grams after an uneventful pregnancy and did not have any health problems other than psoriasis until the date of admission. In his family history, it was learned that the mother of the patient was 42 years old, his father was 45 years old, his father was diagnosed with diabetes at the age of 23, and his grandfather and aunt were also diagnosed with diabetes. Her grandfather and aunt first used insulin therapy and then followed up with oral antidiabetic. In the physical examination at the time of admission, no additional finding was found except for the height 161.4 cm (25-50 p), body weight 62.1 kg (75-90 p), Tanner stage 5, skin psoriasis lesions. In laboratory tests, blood sugar: 299 mg/dl, HbA1C:

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Table 1: Patient's clinical features and blood parameters over time.

	2021-May	2021-August	2022-January
Arterial blood pressure systolic/ diastolic (mmHg)	120/80	110/75	120/70
Body weight (kg)	62.1	62	64
BMI (kg/m^2)	19	20	20
Glycated hemoglobin (mg/dL)	12.3	13.1	9.1
Fasting blood glucose (mg/dL)	299	152	135
C-peptide (ng/mL)	0.4	0.6	0.8
Creatinine (mg/dL)	0.68	0.69	0.66
ALT (U/L)	21	18	24
AST (U/L)	29	27	25
Total cholesterol (mg/dL)	151	147	130
Triglycerides (mg/dL)	85	82	79
LDL cholesterol (mg/dL)	50	48	47
HDL cholesterol (mg/dL)	53	54	58
Microalbuminuria (mg/L)	<5	<5	<5
Urinary ketones	+++	-	-

Table 2: Patient's therapy over time.

	2021-May	2021-August	2022-August
Diabetic ketosis protocol	+	-	
Insulin glargine 100 U/ml	15-20 UI at 10.00 pm	-	15 UI at 10.00 pm
Insulin lispro 100 U/ml	4 UI before breakfast, 6 UI before lunch and 5 UI before dinner		
Oral sulfonylurea		+	+

15.4%, anti-GAD: 2.67 IU/ml, anti-insulin antibody 2.38 IU/ml, c-Peptide: 1.22 ng/ml, insulin: 8.25 and ketone in urine; glucose was '++', diabetic ketosis protocol was applied and total subcutaneous insulin requirement was 0.3 units IU/kg follow-up and was started. A regular treatment plan was established for type 1 diabetes, which included basal-bolus insulin (Table 1, 2). Table 1, 2 and Figure 1 detail the patient's clinical features, blood parameters, and treatment at the initial medical examination. It was thought that MODY could be due to the negative autoantibodies, the diagnosis of diabetes in first-degree family members and the relatively low insulin value at the time of hyperglycemia.

Genetic analysis and clinical follow-up

For analysis, the DNA of the case was isolated by standard procedure. BLK (NM_001330465.2): C.1081G>T (p.Gly361Trp) heterozygous mutation was detected by Sanger sequencing method. With the molecular confirmation of the diagnosis of BLK-MODY, insulin treatments were gradually discontinued in the patient and oral sulfonylurea treatment was started. Unfortunately, the sulfonylurea did not improve glycemic levels, so we adjusted treatment with basal insulin in addition to oral sulfonylurea. With this type of treatment plan, glycemic control is significantly improved. Long-acting insulin therapy only once a day was sufficient and blood glucose levels were not required to be measured before and after each meal. A year and a half passed from the first visit to fixed drug glycemic compensation. In the follow-up of the patient, no signs of hypoglycemia and no complications of diabetes developed. Since MODY is autosomal dominant, the patient was informed by her family. His brother and sister did not show any signs of hyperglycemia, and no mutations were found in genetic tests.

Discussion and Conclusion

In today's world, Next Generation Sequencing (NGS) enables for the simultaneous sequencing of MODY-related genes. So, very quick results can be acquired at a cheaper cost. In young individuals who haven't insulin resistance and obesity, have a significant family history of diabetes, and with negative beta cell antibodies (although a few cases of MODY with positive autoimmunity have been recorded) Monogenic diabetes should be suspected [11,12]. In today's world, Next Generation Sequencing (NGS) enables simultaneous sequencing of MODY-related genes. However, genetic testing is still expensive in most hospitals around the world and should only be requested in severe clinical suspicions [13-16].

To offer adequate prognostic information and regulate the best clinical care and pharmacological therapy for the patient, genetic testing and the discovery of the mutation at the root of the disease are required [17,18]. Moreover, due to the autosomal dominant inheritance that characterizes MODY, all patients diagnosed with the MODY diagnose should get family therapy [19]. The therapy method varies depending on the clinical characteristics and biological reasons of the various kinds of MODY. Young people with maturity-onset diabetes can be treated for many years by diet alone, and sulfonylureas are also advised to be extremely helpful for maintaining glucose levels for many years [20]. Patients with GCK mutations normally do not

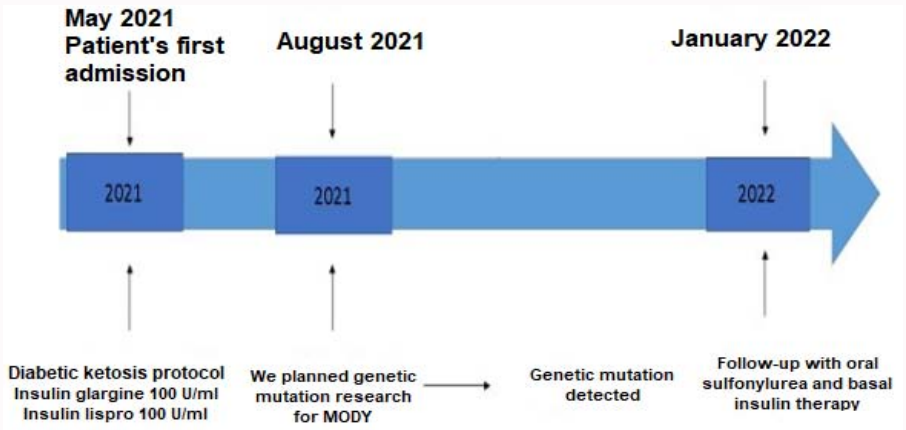

Figure 1: Patient's therapy over time.

require treatment. Patients with HNF1 and HNF4 MODY are more susceptible to sulfonylureas, however they should be supplemented with insulin in the latter stages [21]. In HNF1 MODY patients, those on insulin (7.5%) had higher mean A1C levels than those on oral medicines (6.7%). Sulfonylureas are frequently responsive in patients with HNF1 and HNF4 mutations. Low-dose sulfonylureas (20 mg to 40 mg gliclazide on a regular basis) can let MODY patients live for decades [22,23]. In HNF1 MODY patients, drugs such Nateglinide and Liraglutide reduce postprandial glucose levels [24,25]. Although insulin might be required in some circumstances to provide better glucose control, some people with MODY benefit from oral hypoglycemic medications (e.g., sulfonylureas) instead of insulin. The recommended treatment method for those with blk mutation is insulin, oral hypoglycemic agent and diet. We first started short and long-acting insulin therapy for our patient. We switched to oral sulfonylurea treatment after insulin requirement decreased. Since we could not provide adequate regulation, we combined long-acting insulin therapy with sulfonylurea and we were successful. BLK is a non-receptor tyrosine kinase belonging to the SRC family of proto-oncogenes that stimulates insulin production and release in pancreatic beta-cells by interacting with the transcription factors PDX1 and NKX6.1. A genome wide study of 21 extended United States families segregating autosomal dominant MODY not caused by known MODY genes carried out by Kim led finding locus on chromosome 8p23. They discovered that diabetic patients with MODY linked to 8p23 had a higher prevalence of obesity than diabetic patients with MODY linked to other loci. Mutations in BLK induced diabetes in three families, according to Borowiec. When we look at the literature, the MODY type with BLK mutation reported is very few. MODY should be a diagnosis that must be kept in mind in patients with close family members who have diabetes mellitus, who do not present with severe ketoacidosis despite hyperglycemia, and who have relatively low insulin levels.

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