

## Maturity-Onset Diabetes of Youth Type 4: A Case Report of North of Iran

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### ABSTRACT

Genetically, diabetes can be categorized as polygenic or monogenic. Monogenic diabetes is a heterogeneous group of disorders including NDM, MODY and syndromic diabetes. HNF-4 $\alpha$  (MODY 1), GCK (MODY 2) and HNF-1 $\alpha$  (MODY 3) are the most common forms of MODY. MODY is known by this criterion; Dominant inheritance, NIDDM, and early onset. We report a rare type of MODY that is caused by IPF-1 (MODY 4) mutation.

**Keywords:** Monogenic diabetes, MODY, MODY 4, IPF-1

### INTRODUCTION

Diabetes is generally classified into types 1 and 2, but in addition to these two types, there is a third category of diabetes secondary to non-genetic causes (such as medication, injury and also transplantation) or genetic. The latter type of diabetes is categorized as monogenic diabetes mellitus, which most neonatal diabetes mellitus (NDM) can be considered as, and maturity-onset diabetes of young (MODY) is the most common form of monogenic diabetes [1]. In monogenic diabetes, we have single mutations that can occur by dominant inheritance or due to sporadic mutations [2]. Typically, monogenic diabetes can manifest in three forms of NDM (which can itself be classified into three categories: Transient neonatal diabetes mellitus (TNDM), permanent neonatal diabetes mellitus (PNDM) and syndromic NDM), MODY, and diabetic syndromes. The different phenotypes of patients are related to abnormalities in the genes and their chromosomes [3]. MODY included about 5% of diabetes cases before the age of 45 years [4]. For the first time Tattersall et al. [5] reported a type of diabetes called MODY in 1974. The diabetes was in the mild form and inherited dominantly [6]. MODY genetic analysis was first performed in 1990, which identified five genes including glucokinase (GCK), hepatocyte nuclear factor (HNF4 $\alpha$ ), (HNF1 $\alpha$ ), insulin promoter factor (IPF) and HNF1 $\beta$  as the causes of MODY [7]. MODY is genetically defined as the autosomal dominant with high penetrance and non-insulin dependent (NIDDM) [6]. The classic findings of MODY include the absence of obesity and fat disorders such as dyslipidemia, which can cause insulin resistance. They often experience the disease in the 2<sup>nd</sup> to 4<sup>th</sup> decades, with a history of two successive generations of the disease [8]. To reduce the range of mutations involved in MODY and

NDM, as well as to reduce the costs involved in treating patients, the Sanger sequencing method can be used to sequence common forms of mutation. Sequencing of genes is successful when we know the patients' family as well as the patients' symptoms [9-11], because of low frequency of this type of diabetes always they estimated lower than true incidences and so report of case can help for true diagnosis of then and also better management and consult for family.

### CASE PRESENTATION

We report a patient that was diagnosed at age 14 as a case of MODY4. A 14-year-old girl with hyperglycemia was referred to our diabetes clinic. She was the first child of the family, full term, and was born by cesarean section. There was no history of abortion in her family. The patient's birth weight was 4Kg and her height was 52cm. The duration of breastfeeding was up to 2 years old and complementary feeding was started at age 6 months. She also took vitamin A and D supplements up to 2 years. The patient had a history of hospitalization due to uncontrolled hyperglycemia that was not associated with ketoacidosis and seizure. The patient

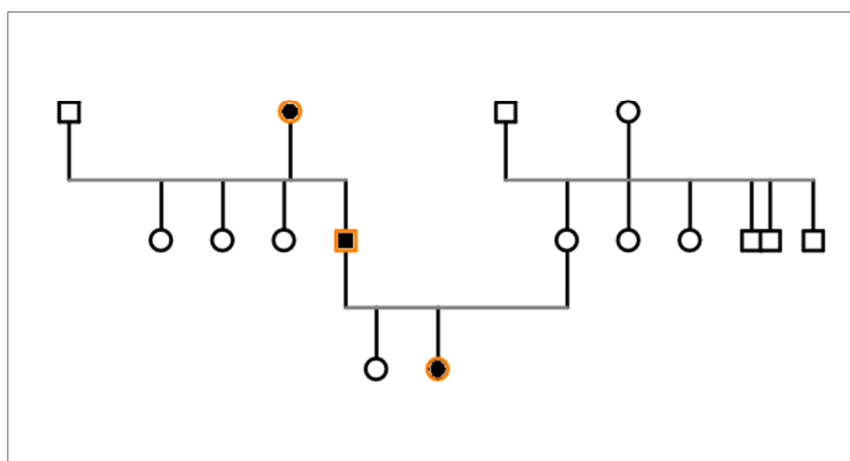
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had no history of underlying disease, especially autoimmune disease. At the time of diagnosis, the patient weight was 57Kg and her BMI was 21.7Kg/m<sup>2</sup> she does not acanthuses, Nigerians. In the patient's family history, her father had hyperlipidemia. On the other hand, there is a history of diabetes in the patient's paternal grandmothers and in all paternal aunts. The patient had no history of weight loss, polyuria, or polydipsia. Her blood sugar profile included 2-hour post prandial blood glucose (2-hpp) or oral glucose tolerance test (OGTT) of 362mg/dl, fasting blood sugar (FBS) of 209mg/dl and hemoglobin A1C (HbA1c) of 11.5%. The patient's lipid profile was total cholesterol of 148mg/dl, low-density lipoprotein (LDL) of 90mg/dl, high density lipoprotein (HDL) of 40mg/dl and triglyceride (TG) of 77mg/dl. Patient's auto-antibodies profile including anti-tyrosine phosphatase ICA 512 (IA2), islet - cell antibodies (ICA) and anti-glutamic acid decarboxylase (GAD) were positive, with values of 13, 3.9 and 9.5, respectively. Also, at

the time of diagnosis, her C-peptide was 2.3ng/ml. Urine analysis encompassed BUN of 14mg/dl, Creatinine of 0.9mg/dl and Urine/Specific Gravity (U/SG) of 1010. The patient was treated with Glibenclamide and Metformin because the first diagnosis was type 2 DM, then Glibenclamide was removed from the patient's regimen and insulin Lantus was added. Due to the lack of precise control of blood sugar, Metformin, insulin Lantus and Novo Rapid were adjusted for the patient, currently being followed with HbA1c of 5.3%. Routine eye examinations were normal and there was no evidence of retinopathy and visual impairment. Renal function was also normal and albuminuria was not reported. It should be noted that the patient also has regular physical activity. Due to strong positive family history of DM, she was evaluated by genetic examine and the find diagnosis MODY 4 because of the result of PDX6, GATA 6 mutation (**Chart 1**).



**Chart 1.** The genealogy of a patient with MODY 4.

## DISCUSSION

Diabetes encompasses a wide range of metabolic disorders due to impaired insulin synthesis, glucose sensing, channelopathy, and impaired endoplasmic reticulum, impairing beta cell expression and function [2,12-14]. In general, diabetes is genetically polygenic, which includes type 1 and type 2 diabetes [12]. But monogenic form includes MODY, NDM (TNDM, PNDM) and syndromic diabetes [2,13,14]. Type 1 diabetes is an early form of autoimmune disease called insulin-dependent diabetes. On the other hand, we have non-insulin-dependent diabetes, which can be polygenic and monogenic, with type 2 diabetes being a type of non-insulin-dependent polygenic diabetes [12, 15]. Non-insulin-dependent monogenic diabetes including NDM, MODY, and rare diabetes-related syndromes [2, 13-15]. The most common mutations involved in NDM are in the KCNJ11 and ABCC8 genes, which are essential for the expression of the ATP-sensitive K-channel in beta cells [16-18]. The octameric structure of

ATP-sensitive K-channel consists of two SUR1 and Kir6.2 subunits, which are encoded by the ABCC8 and KCNJ11 genes, respectively. Each subunit forms half of the central pole channel. The K-channels are blocked by the uptake of glucose metabolism and the increase of the ATP to ADP ratio in beta cells and then by stimulating beta cells and Ca input, insulin granules exocytosed. In fact, mutations involving the K-channel decrease the sensitivity of the channel and lead to open for a longer period of time, resulting in longer hyperglycemia [17]. MODY is one of the non-classic NIDDM, meaning there is a defect in insulin secretion and function. In fact, single gene mutations in beta cells cause the disease to progress slowly [19]. MODY is defined by a specific criterion that is based on the patient's clinical presentation and symptom. Early onset: In fact, at last two family members under the age of 25 may be involved. This cut-off can be changed depending on the number of people in the family, diagnostic tests and anticipation. The anticipation phenomenon has caused that as more and more generations of the family get involved, the

age of the disease decreases. With the development of diagnostic tests, the disease has been diagnosed at an early age [20,21]. On the other hand, involvement in a family member as well as in mild form of diabetes will be diagnosed at an older age, for example, in MODY 3, considering ages 10-60 years [22]. Non-insulin dependent: NIDDM is actually a form of diabetes that is defined by the specified amount of C-peptide or no need for insulin treatment within 5 years after diagnosis. This type of diabetes is suspected in cases of IDDM where a person's hyperglycemic status can be maintained by diet and hypoglycemic agents over a honeymoon period [20].

**Inheritance:** MODY inheritance is an autosomal type that can be dominant or pseudo-dominant. In the dominant inheritance, the single gene is involved. Whereas in the pseudo-dominant, polygenic disorders are involved. Both inheritances can be seen during pregnancy and vertical transmission. The early manifestations of NIDDM in family members are more indicative of a single gene. Autosomal dominant inheritance indicates a positive family history. It is said that most young people with diabetes who have no family history do not have a MODY diagnosis. But some patients miss out on lack of knowledge of their family history [21,23]. More than 10 genes are involved in MODY [24]. Mutations causing MODY are created on different chromosomes. Types 1 to 5 are due defects in chromosomes 20q, 7p, 12q, 13q and 17q, respectively [25]. MODY 1: HNF-4 $\alpha$  acts as an HNF-1 $\alpha$  regulator that plays a role in the function of hormone receptors in the steroid/thyroid branch [24,25]. This type of MODY is present at ages 7-15 years. Although insulin function is not a problem, the first and second phases of insulin secretion are gradually disrupted, with up to 30% of patients requiring insulin treatment over time due to insulin resistance [19,25]. MODY 2: The GCK gene can produce different types of diabetes depending on the type of mutation; MODY (heterozygous mutation) or NDM (homozygous mutation). This mutation creates the most common MODY variant [26,27]. This enzyme functions physiologically as a glucose sensor and plays a limiting enzyme role in the process of insulin secretion in response to glucose uptake in beta cells [28]. These patients have mild hyperglycemia that can progressively lead to insulin resistance, but the vascular complications are not expected because, this mutation is non-progressive [26,29-31]. The diagnosis of these patients is discussed before puberty with blood and urine (glycosuria) tests [30]. Depending on the mutation in the infant and the parents, the infant may have gain weight, loss weight or normal weight [32]. MODY 3: This is the most common variant of MODY in Asia, Europe and North America which is caused by HNF-1 $\alpha$  mutation [29]. It is expressed in various organs such as the liver, kidney and pancreas [33,34]. Unlike GCK mutation, this is a progressive one that decreases pancreatic endocrine secretion in response to stimulation [24]. This MODY is expressed by abnormal glucose tolerance test

(GTT) and insulin resistance in adulthood, which is not apparent before puberty [22]. Due to proximal tubule involvement, the nephropathy was in the form of glycosuria, aminoaciduria, and albuminuria [34]. MODY 4: Like HNF- $\alpha$  factor, the IPF-1 is involved in both the development and function of beta cells [35,36]. Mutation of this gene may produce different types of diabetes depending on the endocrine or exocrine involvement. If the disorder is purely endocrine disruption, MODY 4 is created and if it is both endocrine and exocrine, PNDM is created [37,38]. For the first time in 1997, MODY 4 was identified due to the heterozygous mutation of IPF-1 [36]. Of the endocrine regulators of the IPF-1, its role in the expression of the somatostatin, GCK, GLUT2 and pre-pro insulin genes has been noted [39]. The clinical signs of MODY 4 are similar to MODY 1 [40]. The most prominent characteristic of MODY 4 is hyperinsulinemia and obesity at an early age that can misdiagnose as type 2 DM [41]. In MODY diagnosis, clinical findings were used to confirm the disease and laboratory data were also used to rule out other types of diabetes. Clinical findings include age at onset of disease, non-insulin dependency, autosomal dominant inheritance, BMI, and laboratory data such as islet auto-antibody, OGTT and serum C-peptide levels [42,43]. The auto-antibodies used in the diagnosis of diabetes include antibody against islet antigen 2. Glutamic acid decarboxylase and islet cell [44]. Auto-antibodies are not a reliable criterion because patients have been found to have diabetes despite low auto-antibody titration and, On the other hand, auto-antibody titration decreases as the disease progresses. C-peptide is not a sufficient criterion for diagnosis because in patients with early and chronic diabetes, a level of C-peptide was found discriminable [45]. In the HNF-4 $\alpha$  mutation, all of the patients' lipid profile decreased but LDL increased [46,47]. In patients with GCK mutation, an increase in HbA1c as well as decrease in lipid profile (HDL-cholesterol) is seen compared to the normal state [48]. Among patients with the HNF-1 $\alpha$  and GCK mutations, patients with the HNF-1 $\alpha$  mutation have significantly lower CRP [49]. Genetic analysis is performed on MODY patients when a young non-obese child with a positive family history] and abnormal tests such as FBS, OGTT and negative auto-antibody that does not experience any stress [50]. The evaluation of phenotypic variant of dominant gene has shown that common mutations cause less impairment in beta cell function and plasma glucose [51]. About 80% of MODY cases are caused by the three genes HNF-4 $\alpha$ , HNF-1 $\alpha$  and GCK [41]. Only these three genes are examined for MODY screening in pregnant women [33]. In the MODY patients, timely identification of patients with the aim of reducing vascular complications and insulin resistance is important [27]. One of the vascular complications in MODY patients is nephropathy. Among the MODY cases, mild hyperglycemia in MODY 2 rarely progresses to vascular complications [26,29]. MODY 1 and 4 due to poor control glycaemia are susceptible for leading to nephropathy [24,26,27,40].

MODY 3 patients have both micro and macro vascular complications [22,52]. On the other hand, renal involvement in these patients falsifies a syndrome similar to Fanconi [34]. MODY diagnosis can also be made on the basis of treatment, as young people with diabetes who are not obese respond to treatment with sulphonylureas [53]. In cases of k-channel mutations. Sulphonylurea is preferable to insulin because the patient experiences shorter periods of hypoglycemic. Also, a comparison of HbA1c induced by two drugs has shown that patients taking sulphonylurea have better glycemic control [16,54]. Treatment of patients with the GCK mutation does not decrease glucose levels and HbA1c because treatment of these patients decreases endogenous insulin secretion [55]. Treatment of patients with HNF-1 $\alpha$  mutation is initiated with low dose sulphonyl urea [46]. If treatment with sulphonyl urea is not effective in patients with HNF-1 $\alpha$  and HNF-4 $\alpha$  mutations, insulin, dipeptidyl peptidase-4 (DPP-4) and glucagon-like peptide-1 (GLP-1) receptor agonist can be used [56]. Insulin and oral hypoglycemic agents (OHA) can be effective in patients with IPF-1 mutation [57,58]. As a result, depending on the genes mutations, patients develop different types of MODY that will have different approaches and treatments [59-62].

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