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CASE REPORT

Maturity Onset Diabetes of the Young is Not Necessarily Associated with Autosomal Inheritance: Case Description of a De Novo HFN1A Mutation

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ABSTRACT

Maturity onset diabetes of the young (MODY) accounts for up to 4% of all cases of diabetes in pediatric patients. MODY is usually characterized by autosomal dominant inheritance, impaired insulin secretion, and an average age at diagnosis of 18–26 years. Mutations in the hepatocyte nuclear factor 1-alpha (HNF1A), glucokinase, hepatocyte nuclear factor 4-alpha, and hepatocyte nuclear factor 1-beta genes are the mutations most frequently observed in cases of MODY. We herein report a case of HNF1A-MODY characterized by an early onset of diabetes. Genetic investigations revealed a de novo heterozygous substitution, N237D (HNF1A c.709A>G), in exon 3 of the HNF1A gene. Our case supports the hypothesis that de novo mutations are more frequent than expected. This recent evidence may suggest that conventional clinical diagnostic criteria for MODY should be revised and personalized according to the individual patient.

Keywords: Genetic testing; Hepatocyte nuclear factor 1-alpha; Hyperglycaemia; Inheritance; MODY; Missense mutation; Next-generation sequencing

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INTRODUCTION

Maturity onset diabetes of the young (MODY) accounts for between 1 and 4% of all cases of diabetes in children and adolescents [1–4]. MODY is a monogenic form of diabetes characterized by autosomal dominant inheritance, impaired insulin secretion, and an early age at diagnosis—typically under 25 years of age [5, 6]. To date, abnormalities in at least 13 genes on different chromosomes have been described [7]. Molecular genetic testing is needed to confirm a diagnosis of MODY, predict the likely clinical course, define risk for relatives, and determine treatment [8]. Mutations in the hepatocyte nuclear factor 1-alpha (HNF1A), glucokinase (GCK), hepatocyte nuclear factor 4-alpha (HNF4A), and hepatocyte nuclear factor 1-beta

(HNF1B) genes are the mutations most frequently observed in cases of MODY. HNF1A and GCK mutations are the most common causes of MODY in Caucasian populations [9, 10]. HNF1A-MODY, also known as MODY 3, prevails in the United Kingdom, the Netherlands, and Germany [11–14]. Its clinical phenotype is heterogeneous and varies according to environmental and/or genetic factors [15]. Generally, HNF1A-MODY manifests itself during the postpubertal and young adult periods; the average age at diagnosis is 18–26 years. Hyperglycemia is the result of progressive beta-cell function deterioration over time in the absence of clinical signs of insulin resistance. During the early stages of the disease, an oral glucose tolerance test (OGTT) can be performed to check for a marked increase in glycemia (> 5 mmol/l). Rarely, this type of MODY becomes apparent with mild-to-moderate ketoacidosis that is clinically indistinguishable from the onset of type 1 diabetes. Glycosuria is often present and it is related to a low renal threshold, typically lower than 10 mmol/l [16]. Low-dose sulfonylurea therapy permits effective glycemic control among individuals with HNF1A-MODY by stimulating the existing beta-cell reservoir. An increased risk of microvascular and macrovascular complications in HFN1A-MODY patients has recently been highlighted [17, 18].

In the case reported in the present paper, we identified a de novo heterozygous substitution, N237D (HNF1A c.709A>G), in exon 3 of HNF1A in a MODY 3 patient. This mutation was already known to be a MODY pathogenic variant according to the VarSome database. Written informed consent was obtained from the patient's parents for the publication of this case report.

CASE PRESENTATION

A 10-year-old female child, the third born to nonconsanguineous parents, was admitted to our clinic with a recent history of polyuria, polydipsia, and headache. The family history was negative for any form of diabetes, but positive for another autoimmune disease (her mother was affected by Hashimoto's thyroiditis). At the age of 6 years she had been surgically treated for hepatic cystic echinococcosis. She was in a good clinical state at admission, and a general examination showed no abnormalities. A physical examination evidenced normal growth parameters and blood pressure. Laboratory tests showed the following results: glycemia 21.4 mmol/l, glycated hemoglobin (HbA1c) 94 mmol/mol (normal value 20–48 mmol/mol). Her acid-base balance was normal (pH 7.39, serum bicarbonate 23 mmol/l). Ketonemia and ketonuria were negative. Plasma basal C-peptide and stimulated C-peptide after an intravenous glucagon load were, respectively, 1.07 ng/ml (normal value 1.0–3.0 ng/ml) and 2.52 ng/ml (normal value 3.0–9.0 ng/ml). Abdominal ultrasound was negative for hepatic lesions and/or renal abnormalities. Multiple daily insulin treatment was started, with an initial total insulin dosage of 0.8 IU/kg, insulin lispro at meals, and insulin glargine at bedtime. Tests for antibodies against insulin, glutamate decarboxylase (GAD), tyrosine phosphatase (IA2), islet cells (ICA), and zinc transporter 8 (ZnT8) were all negative. HLA did not predispose the patient to type 1 diabetes. During the first 6 months of follow-up she maintained her HbA1c values above 53 mmol/mol. Her glycemic control was not optimal since it was characterized by broad glycemic variability. On the suspicion of monogenic diabetes, genetic testing was performed. The genetic analysis revealed a de novo heterozygous substitution, N237D (HNF1A c.709A>G), in exon 3 of the HNF1A gene in the proband. This substitution was not present in her parents. The biological relationship of the proband to her parents was confirmed by microsatellite analysis.

Once HNF1A-MODY had been diagnosed, we suspended insulin therapy and started treatment with gliclazide at 1.4 mg/kg. We observed a prompt improvement in the patient's glycemic control after the first few days of the new therapeutic approach. During the subsequent 6 months of follow-up, her mean glycosylated hemoglobin was 44 mmol/mol.

DISCUSSION

The HNF1A gene is located at chromosome 12q24, comprises 10 exons that span 23,790 bp, and encodes a 631-amino-acid protein which is expressed in many tissues such as the liver, kidney, and pancreas [19]. In pancreatic beta cells, HNF1A plays a regulatory role in the expression of several genes involved in glucose metabolism and transport, such as glucose transporter 2 (GLUT2) and pyruvate kinase [20, 21]. One of the first direct studies of human islets from an individual with a heterozygous missense variant in the HNF1A locus confirmed that loss-of-function variants of HNF1A lead to insulin-insufficient diabetes not through a significant loss of beta-cell mass but rather by impacting beta-cell transcriptional regulatory networks, resulting in the impairment of beta-cell pathways that are needed for a normal insulin response to glucose [22]. Heterozygous mutations of HNF1A that cause diabetes were first identified in 1996, and more than 400 different mutations have since been described [23]. These mutations include missense and nonsense mutations, insertions and duplications, deletions, insertion/deletions, promoter region mutations, and splice site mutations [24]. These mutations occur throughout the gene, but they are mainly found in exon 2 (0.33 mutations per nucleotide) and in exon 4 (0.28 mutations per nucleotide). A high proportion of the mutations, particularly missense mutations, involve the dimerization and DNA-binding domains, which seem to be less tolerant of minor structural changes [25]. The type and the location of the mutation seem to be linked to the age at diabetes diagnosis. Mutations involving the first six exons are correlated with an earlier diagnosis (median age of 18 years) than mutations located in either exons 8–10 or the transactivation domain (median age of 30 years) [26]. Patients with truncating mutations are diagnosed at an average age of 20 years regardless of the location of the mutation within the HNF1A gene [27, 28].

The gold standard method of screening for mutations is sequence analysis of the coding regions and conserved splice sites [29]. In patients with a very specific clinical phenotype, Sanger sequencing, also called the chain termination method, may be sufficient to identify abnormalities of the selected gene [4]. The recent introduction of targeted next-generation sequencing (NGS)—which permits the sequencing of gene collections, exomes, or even whole genomes—has led to an increase in the number of patients diagnosed with monogenic diabetes [30].

To our knowledge, the c.709A > G HNF1A missense mutation has only been identified in one family before [31]. As regards the clinical aspects of the mutation, our patient was diagnosed at the age of 10 years. Diabetes onset was characterized by classic symptoms: hyperglycemia and a HbA1c value of 94 mmol/mol in the absence of ketoacidosis. The switch from insulin to sulfonylurea treatment was successful and led to good glycemic control. This clinical course demonstrated that this type of mutation seems to be related to a very early deterioration of beta-cell function, which can lead to the onset of diabetes during the first decade of life. The prompt response to gliclazide treatment is in accord with the evidence of sulfonylurea sensitivity in the majority of HNF1A diabetic patients [32].

De novo MODY mutations are conventionally considered rare. The American Diabetes Association and various clinical centers for monogenic diabetes have created and published general guidelines, recommendations, and algorithms which suggest that DNA analysis should be performed only if patients have a family history of at least two generations with hyperglycemia or diabetes [7, 33–35]. Nevertheless, some recent epidemiological studies have demonstrated that de novo mutations of the major MODY genes could be more frequent than previously assumed. Stanik et al. described 11 de novo mutations of GCK, HNF1A, and HNF4A in 150 probands (16.3% of the entire cohort of 922 patients) who fulfilled all of the MODY criteria except for the family history of diabetes or hyperglycemia. Four of these de novo mutations involved the HNF1A gene [36]. Yorifuji et al. analyzed the four major MODY genes in a cohort of 263 Japanese patients with early-onset, non-obese, MODY-like diabetes.

Those authors discovered that 13.8% of the patients were mutation positive and did not have affected parents. Five of the 19 reported de novo mutations are of the HNF1A gene [37]. This recent evidence could cast doubt on the validity of one of the clinical characteristics most commonly used for MODY diagnosis—a family history of at least two unilateral consecutive generations with diabetes or hyperglycemia. Therefore, in order to minimize misdiagnosis, clinical diagnostic criteria should be revised and personalized according to the individual patient.

CONCLUSION

Our case supported the hypothesis that de novo mutations are not as rare as expected. More epidemiological studies, especially those incorporating NGS investigations, should be implemented as a means to identify the clinical features and biomarkers that are typical of MODY patients, allowing the development of clinical approaches to the selection of patients for testing that have the optimal combination of sensitivity and specificity.

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Compliance with Ethics Guidelines. Written informed consent was obtained from the patient's parents for the publication of this case report.

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