Research article

Molecular Diagnosis of Monogenic Diabetes and Their Clinical/Laboratory Features in Turkish Children

Running Head: Monogenic Diabetes in Turkish Children

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What is already known on this topic?
Monogenic diabetes is a heterogeneous group of disorders, accounting for just 1%–6% of all diabetes. Variants in *HNF1A, HNF4A*, and *GCK* are representing most of MODY-monogenic diabetes cases. Patient numbers and information are limited on less common causes of monogenic forms of diabetes.

What this study adds?
This study is the first Turkish multicenter genetic study of the patient with monogenic diabetes. This study determines the clinical and laboratory features, the admission characteristics and distribution of monogenic diabetes in childhood.

ABSTRACT
Introduction: Monogenic diabetes is a heterogeneous disease that causes functional problems in pancreatic beta cells and hyperglycemia. The aim of this study is to determine the clinical and laboratory features, the admission characteristics and distribution of monogenic form of diabetes in childhood.
Method: Patients aged 0-18, who were molecularly diagnosed with monogenic diabetes, and accepted to participate in the study, were included in the study.
Results: 77 female and 92 male cases with a mean age of 8.18 ± 5.05 years at diagnosis were included. 52.7% of the cases were diagnosed with monogenic diabetes by random blood glucose measurement. The reason for genetic analysis in 95 (56.2%) of cases was having a family member diagnosed with diabetes under the age of 25. At the time of diagnosis, ketone was detected in urine in 16.6% of the cases. Mean HbA1c in admission; fasting blood glucose, fasting insulin, c-peptide values were 7.3 ± 2.1%, 184.9 ±128.9 mg / dl; 9.4 ± 22.9 IU / L; 1.36 ± 1.1 ngm / L; respectively. GCK-MODY was found in 100 (59.2%) of the cases, HNF1A-MODY in 31 (18.3%), *ABCC8* in 6 (3.6%), *KCNJ11* in 5 (3%), *HNF4A* in 2 (1.2%), and *HNF1B* in 2 (1.2%).
Conclusion: Recent studies have indicated HNF1A-MODY as the most frequent of all the MODY-monogenic diabetes cases in the literature (50%), while GCK-MODY as the second most frequent with 32%. In our study, 59.2% of the patients were GCK, and 18.3% were HNF1A-MODY, despite the literature data.
Keywords: monogenic diabetes, early-onset diabetes, next-generation sequencing, *GCK, HNF1A*

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Introduction
Monogenic diabetes is a monogenic, clinically and genetically heterogeneous form of diabetes. This includes neonatal diabetes mellitus (NDM), maturity onset diabetes of the young (MODY) and rare diabetes-associated syndromes due to defects in beta cell function. The disease may be inherited within families as a dominant, recessive, or non-Mendelian trait or may present as a spontaneous case due to a de novo variant. Well over 40 different genetic subtypes of monogenic diabetes have been identified to date, each having a typical phenotype and a specific pattern of inheritance (1). The acronym MODY was used to highlight its firm hereditary basis (2).
MODY is estimated to account for only about 1–2% of all cases attributed with diabetes, and usually is misclassified as Type 1 or Type 2 diabetes (3,4). Previously, 13 MODY subtypes were identified, and recently a 14th subtype, is caused by heterozygous variant in the *APPL1* gene, has been added to the list, which have in common a primary defect in insulin secretion associated with pancreatic beta cell dysfunction (5). Heterozygous variants in the *GCK* (glucokinase) (MODY 2), *HNF1A* (hepatocyte nuclear factor 1 alpha) (MODY 3), and *HNF4A* (hepatocyte nuclear factor 4 alpha) (MODY 1) genes are the most frequent, and together they account for over 95% of the known genetic causes of MODY. The relative frequencies of MODY subtypes show variations according to the countries using different selection criteria for patients for genetic testing (6).

The aim of the study is to determine the clinical and laboratory features, the admission characteristics, and distribution of monogenic diabetes in childhood in Turkey.

Materials and Methods

Subjects

In this multicenter genetic study, the data of 169 participants were cross-sectionally analyzed. A nation-wide web-based CEDD-NET Data System (http://cedd.saglik-network.org/) was used for data collection between March 2016 and April 2017. Written informed consent was obtained from all subjects, and the study was approved by Gülhane Military Medical Academy, Ethics Committee at 17.02.2016 (Number: 50687469-1491-191-16/1648-409).

A total of 169 patients aged 0-18, who were molecularly diagnosed with monogenic diabetes were enrolled. The suspected clinical diagnoses of monogenic diabetes were based on (1) the early onset of diabetes (25 years of age); (2) negative pancreatic autoantibodies, (3) persistently detectable C-peptide, low or no insulin requirement 3 years after the diagnosis or dominant inheritance or incidental hyperglycemia.

Clinical data of the patients, including gender, age at diagnosis, and family history of diabetes (e.g. diabetic complications and treatments), were obtained through medical records during hospitalization. Laboratory data at diagnosis, including blood glucose, insulin, C-peptide, glycated hemoglobin (HbA1c), and autoantibodies were collected as well.

Genetic Studies

To confirm the diagnosis of monogenic diabetes, genetic tests were performed in various genetic laboratories and entered to the statistics program by the centers participating in the study. Sequence variants were analyzed by VarSome (7), and classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines (8). Variants evaluated as pathogenic and likely pathogenic according to ACMG criteria were included in the study.

Statistical Analysis

Data analysis was performed with IBM-SPSS for Windows software (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Descriptive statistics of the clinical and laboratory findings were expressed as mean ± standard deviation (SD), number, and percentage. Since the number of patients in most subgroups were few and not homogeneously distributed, comparative statistics were not performed in order to avoid type 2 statistical errors.

Results

A total of 169 patients, 92 males (54.4%) and 77 females (45.6%), were included in the study. The mean age of the patients at diagnosis was 8.18 ± 5.05 years. The mean **birth** weight was 3110 ± 660 g and the mean gestation week was 38.5 ± 2.1 weeks. Presenting complaints included: incidental diagnosis in 89 patients (52.7%), polyuria and polydipsia in 50 (29.6%), diabetes history in family in 14 (8.3%), weight loss in 5 (3%), and obesity in 2 (1.2%). Five patients (3%) were diagnosed with ketoacidosis and 12 patients (7.1%) with ketosis at initial evaluation. All patients had no additional features such as renal cysts.

Initial treatment consisted of diet alone in 93 patients (55%), diet and insulin treatment in 62 (36.7%), and diet and an oral anti-diabetic drug in 13 (7.7%). Oral antidiabetic drugs given to the patients at their follow-ups; sulfonylurea in 34 (20.1%), whereas 10 (5.9%) received metformin, and one (0.6%) repaglinide.

GENETIC FINDINGS

The distribution of the variants was as follows: *GCK* (MODY 2) in 100 patients (59.2%), *HNF1A* (MODY 3) variants in 31 patients (18.3%), *ABCC8* variants in 6 patients (3.6%), *KCNJ11* variants in 5 patients (3%), *INS* in 4 patients (2.4%), *HNF4A* (MODY 1) in 2 patients (1.2%), *BLK* (MODY 11) in 2 patients (1.2%), *HNF1B* (MODY 5) in 2 patients (1.2%), *NEUROD1* (MODY 6) in one patient and *CEL* (MODY 8) in one patient. Genetic diagnosis was not specified in 15 cases and further genetic analysis was planned (Figure 1).

The reason for requesting genetic analysis in 95 (56.2%) of the cases was having a family member diagnosed with diabetes under the age of 25, while in 89 (52.2 %) of the cases was autoantibody negativity at the time of diagnosis, in 15 (8.9%) of the cases was that diabetes was diagnosed before 6 months of age.

CHARACTERISTICS OF PATIENTS WITH A *GCK* VARIANT

In patients with a *GCK* variant (41 females and 59 male), mean age at diagnosis was 8.55±4.66 years, mean birth weight was 3160±460 g, mean gestation week was 38.9±1.2. Anthropometric data and laboratory characteristics of GCK-MODY patients at baseline are summarized in Table 1. Almost 67% of the cases were diagnosed with GCK-MODY by random blood glucose measurement. None of the patients had ketonemia/ketonuria, ketoacidosis, or dyslipidemia at the time of diagnosis or during the follow-up. Of all the patients, 91 had impaired fasting glycemia (IFG), and nine had impaired glucose tolerance (IGT). Forty (40%) of the patients had typical family history of diabetes in three generations. Sixty-two (62%) of the patients' parents had been diagnosed before the age of 25 years. Nineteen (19%) of the patients' mothers were diagnosed during pregnancy. Initial treatment consisted of diet alone in 74 patients (74%), diet and insulin treatment in 19 (19%); and diet and an oral anti-diabetic drug in 7 (7 %). Oral anti-diabetic drugs were introduced to the patients at their follow-ups; sulfonylurea in 13 patients (13%), whereas 5 (5%) received metformin.

CHARACTERISTICS OF PATIENTS WITH A *HNF1A* VARIANT

In patients with a *HNF1A* variant (17 females and 14 male), the mean age at diagnosis was 10.1±3.6 years, mean birth weight was 2870±630 g, and mean gestation week was 38.4±2.52. Anthropometric data and laboratory characteristics of HNF1A-MODY patients at baseline are summarized in Table 2. Nine (29%) of the patients had ketonemia/ketonuria, none of the patients had ketoacidosis at the time of diagnosis or during follow-up. Only 6% of the cases were diagnosed with HNF1A-MODY by random blood glucose measurement. Thirteen (54.8%) of the patients had typical family history of diabetes in three generations. Twenty-three (74.2%) parents had been diagnosed before the age of 25 years. Five mothers were diagnosed during pregnancy. Initial treatment consisted of diet alone in 9 patients (29%), diet and insulin treatment in 19 (61.3%), and diet and an oral anti-diabetic drug in 3 (9.7%). Oral antidiabetic drugs were initiated at the patients' follow-ups; sulfonylurea for 34 patients (20.1%), whereas 10 (5.9%) received metformin, and one (0.6%) repaglinide.

CHARACTERISTICS OF PATIENTS WITH VARIANTS IN OTHER GENES

In the present study, there were *ABCC8* variants in 6 patients (3.6%), *KCNJ11* variants in 5 patients (3%), *INS* in 4 patients (2.4%), *HNF4A* (MODY 1) in 2 patients (1.2%), *BLK* (MODY 11) in 2 patients (1.2%), *HNF1B* (MODY 5) in 2 patients (1.2%), *NEUROD1* (MODY 6) in one patient, and *CEL* (MODY 8) in one patient. The genetic diagnosis was not specified in 15 cases. The reason for requesting genetic analysis in patients with *ABCC8* variants was; being diagnosed before 6 months of age in three cases (50%), having a family member diagnosed with diabetes under the age of 25 in two cases, diagnosis of non-obese type 2 diabetes in one. Two of the patients had diabetic ketosis at the initial evaluation, while the other four did not. The aforementioned two were on sulphonylurea therapy, while the other four continued on the prior insulin regimen. The reason for requesting genetic analysis in all the patients with *KCJN11* variants was so that the patients were diagnosed before 6 months of age. Two of these patients were diagnosed with diabetic ketoacidosis. Sulfonylurea treatment was administered to all the patients and the treatments were continued during their follow-up. The reason for requesting genetic analysis in *INS* was due to diabetes being diagnosed before 6 months of age. Three of these patients were diagnosed with diabetic ketosis, and all these patients were given insulin and continued this therapy. The patients with *HNF4A* (MODY 1) were diagnosed with impaired glucose tolerance without ketone in urine. After the genetic results of the patients were obtained, the initial insulin therapy was terminated, and oral anti-diabetic treatment was initiated. The two patients with *BLK* (MODY 11) were diagnosed with diabetes due to polyuria, polydipsia. One of the patients had diabetic ketosis and, therefore, no response to sulfonylurea treatment, the initial treatment was replaced with insulin therapy. The other patient with the *BLK* variant had no ketosis and responded to the sulfonylurea treatment. One of the two patients with *HNF1B* variant was diagnosed with diabetes due to polyuria, polydipsia at the age of 12.7 (HbA1c: 6.8%) and insulin treatment was deemed unnecessary during the follow-up. As for the other patient who was diagnosed with diabetes due to polyuria, polydipsia with ketosis at the age of 8.1 (HbA1c: 11.2 %), insulin therapy was necessary throughout the follow-up period. The patient with NEUROD1 (MODY 6) had the initial complaint of polyuria with impaired fasting glycemia. BMI of the patient was 18.51 kg/m2 and HbA1c, at the time of diagnosis, was 5.6 %. The patient was monitored as their diet was regulated, before the admission of a treatment. The patient with *CEL* (MODY 8) variant was diagnosed by random blood test measurement (HbA1c: 8.7 %,) and sulfonylurea treatment was initiated. After one-year of oral anti-diabetic therapy, since the HbA1c value was 10.8 %, insulin treatment was deemed necessary.

Discussion

The relative frequencies of monogenic forms of diabetes show variations according to the countries where the studies took place. For example, MODY 3 is the most common subtype in the United Kingdom, The Netherlands, Denmark, and Norway, but MODY 2 is the most common in Germany, Austria, Poland, the Czech Republic, Italy, Greece, and Spain (6). In our study, MODY 2 was the most frequently detected subtype (59.2 %). These differences may be explained using different selection criteria for patients for genetic testing (6)

GCK-MODY is one of the commonest subtypes of monogenic diabetes in the pediatric diabetes clinic and its clinical phenotype is remarkably homogeneous among patients (9). The patients show non-progressive mild hyperglycemia from birth. Their HbA1c is mildly elevated but usually below 7.5% (10). Same as recent studies, the mean HbA1c value of our GCK-MODY patients was 6.4%. Because blood glucose does not deteriorate significantly over time, this subtype of monogenic diabetes is rarely associated with complications of diabetes and patients do not generally require any treatment (11). For most cases, diet alone is sufficient to achieve metabolic control (12). However, due to incompatibility with diet therapy, oral anti-diabetic drugs (18%) and insulin regimen (19%) were added to the treatment of patients.

HNF1A-MODY is the most common form of monogenic diabetes that results in familial symptomatic diabetes (13). Almost 94 % of the cases were diagnosed as HNF1A MODY with a symptomatic finding like recent studies. Over time, fasting hyperglycemia and osmotic symptoms (polyuria, polydipsia) present but patients rarely develop ketosis because some residual insulin secretion persists for many years (14). In our study, 29 % of the patients had ketosis and the treatment was consisted of insulin treatment or an oral anti-diabetic drug in addition to diet therapy in 71 % of these patients. The development of chronic complications of diabetes is related to the degree of metabolic control (14). None of our patients developed complications.

GCK (MODY 2), *HNF1A* (MODY 3), and *HNF4A* (MODY 1) genes are responsible for many genetic causes of monogenic diabetes (6). The other monogenic forms of diabetes have been shown to represent together only a small proportion (<5%) of cases but molecular confirmation of the diagnosis prevents unnecessary insulin treatment in patients with monogenic diabetes and improves both metabolic control and quality of life (15). Sulfonylurea treatment was started for all the patients with *KCJN11* variants and this treatment was continued during their follow-up. One-third of the patients with *ABCC8* variants continued sulfonylurea treatment alone while all INS-MODY patients were initiated insulin therapy and continued this therapy. In a single-center study on monogenic diabetes conducted in Turkey, half of the patients with the *ABCC* variant and the patient with the *KCJN11* were receiving sulfonylurea therapy, while the patient with the *INS* variant was on insulin regimen (16).

Family history is crucial for requesting genetic analysis for monogenic diabetes such as diagnosis of diabetes under the age of 25 years in at least one family member, autosomal dominant inheritance pattern through at least three generations, or the existence of at least two first-degree relatives with diabetes (17). In our study, having a family member diagnosed with diabetes under the age of 25 was the most frequent reason for requesting genetic analysis (56.2%). These prediction models show high sensitivity, although with relatively low positive predictive values that result in even higher proportions of variant-negative cases, however, it leads to the diagnosis of the more rare monogenic forms of diabetes and to distinguish it from diabetes type 1 or type 2 to avoid the unnecessary insulin or sulfonylurea treatment, which may severely affect the patient's health.

Study Limitations

Detection of all case data for the whole country was incomplete and naturally some findings were not declared. Moreover, laboratory and genetic tests were analyzed in different centers. There may also be bias in terms of case determination in different centers. Finally, lack of the standardized approach in the management of diabetes was one of the limitations of the study.

Conclusion

This is the first Turkish multicenter genetic study of the children with monogenic diabetes. In this study we tried to determine distribution, clinical and laboratory features of monogenic diabetes. Our study showed that random blood glucose measurement had an important place in diagnosis and the most common reason leading to genetic analysis was having a family member diagnosed with diabetes at a young age. Moreover, the study results may contribute to a better understanding of the pathogenesis of the most common subtypes of monogenic diabetes and to a more personalized approach to patients' treatment, follow-up, and genetic counselling.

Ethics

Ethics Committee Approval: The study was approved by Gülhane Military Medical Academy, Ethics Committee at 17.02.2016 (Number: 50687469-1491-191-16/1648-409)

Informed Consent: Written informed consent was obtained from all participants or their parents/guardians.

Authorship Contributions

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Table 1: Anthropometric and laboratory characteristics of GCK-MODY patients (n = 100)

Age, year	12.24±5.29
Age at the time of diagnosis, year	8.55±4.66
Female/male, n	41/59
Body mass index (kg/m^2)	17.3±3.31
Birth weight, g	3160±467
Gestation week, wk	38.9±1.2
Fasting blood glucose, mg/dL	127.8±30.7
Fasting insulin, IU/L	8.95±24.15
HbA1c, %	6.40±0.48
C-peptide, ng/mL	1.39±1.05

Table 2: Anthropometric and laboratory characteristics of HNF1A-MODY patients (n = 31)

Age, year	14.04±3.43
Age at the time of diagnosis, year	10.1±3.6
Female/Male, n	17/14
Body mass index (kg/m^2)	19.56±4.15
Birth weight, g	2870±630
Gestation week, wk	38.4±2.52
Fasting blood glucose, mg/dL	218±111
Fasting insulin, IU/L	10.5±7.3
HbA1c, %	8.5±2.5
C-peptide, ng/mL	1.61±0.99

Figure 1: The distribution of the variants causing monogenic forms of diabetes