P2-P070

Frequency and etiologic spectrum of monogenic diabetes in pediatric age in a single academic center

Jin-Ho Choi[1], Arum Oh[1], Go Hun Seo[1], Gu-Hwan Kim[2], Han-Wook Yoo[1,2]
[1]Department of Pediatrics, [2]Medical Genetics Center, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

Introduction

- Monogenic diabetes mellitus (DM) is a single gene disorder caused by mutations in genes that control either the production or release of insulin.
- Monogenic DM comprises a large spectrum of phenotypes including neonatal diabetes mellitus (NDM), maturity-onset diabetes of the young (MODY), and rare syndromic diabetes with extra-pancreatic features.
- Prevalence of monogenic DM is estimated for about 1%–5% of all patients with DM. Overlapping clinical features of various forms of diabetes make differential diagnosis challenging.
- Recent advances in molecular genetics contributed to the identification of the genetic etiologies of many subgroups of monogenic diabetes.

Objectives

- This study was performed to investigate frequency and genetic etiologies of monogenic diabetes in a single academic center.

Methods

- This study included 466 consecutive patients with DM diagnosed before 18 years of age from January 1996 to July 2017.
- Clinical features, biochemical findings, β-cell autoantibodies, and molecular characteristics were reviewed retrospectively.
- Molecular analysis of causative genes of monogenic diabetes was performed according to the clinical phenotype of each patient.

Results

Etiologic distribution of diabetes mellitus

- Three hundred and thirty two patients (71.2%) had type 1 DM, while 108 patients (23.2%) were type 2 DM.
- Genetic etiologies were identified in the remaining 26 patients (5.6%).

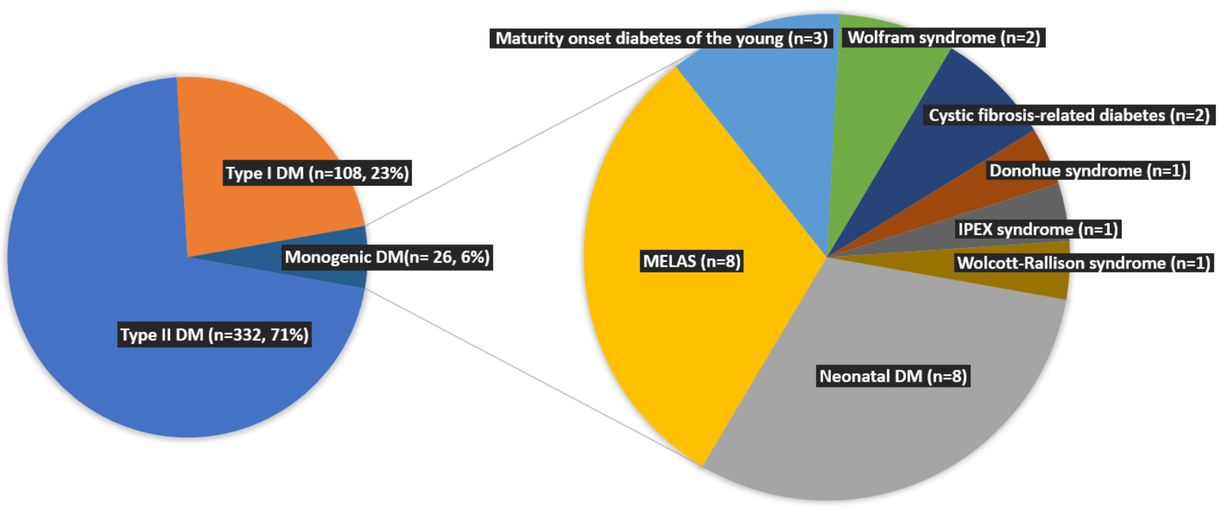


Fig. 1. Frequency and etiologic spectrum of diabetes mellitus in this study

Eight patients with neonatal diabetes mellitus

- Two patients were diagnosed with transient NDM caused by paternal uniparental disomy of 6q24.
- The other six were permanent form with mutations in K_{ATP} channel genes. Among them, a male was misdiagnosed with type 1 DM at the age of 50 days; however, at age 17.9 years, he was suspected to have DEND syndrome due to global developmental delay and seizure. A heterozygous p.R201H mutation in *KCNJ11* was identified, and insulin therapy was successfully switched to sulfonylurea.

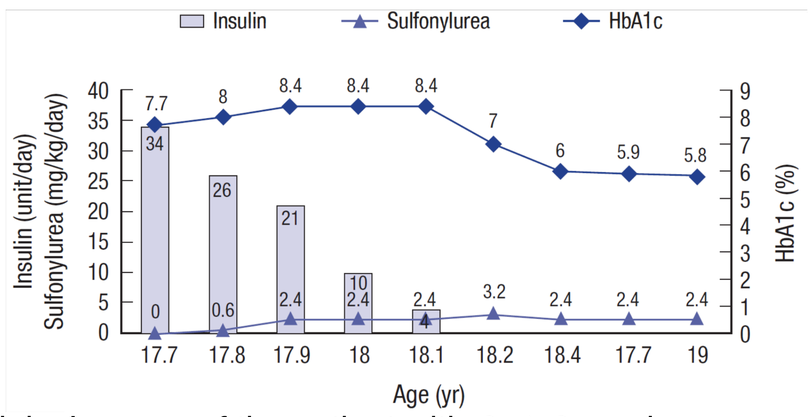
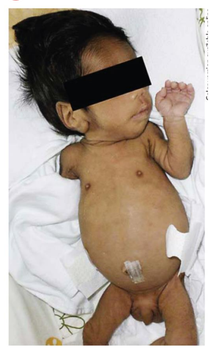


Fig. 2. The clinical course of the patient with DEND syndrome.

A male with Donohue syndrome with two novel mutations

- A male, the first child of nonconsanguineous parents, presented with fasting hypoglycemia and postprandial hyperglycemia. He showed with acanthosis nigricans, hirsutism, high insulin level, and intrauterine growth retardation. He was compound heterozygous for the p.R1066* and p.Q1232* mutations in *INSR*.



Two siblings with Wolfram syndrome

- Bilateral optic atrophy and urinary incontinence at adolescent period
- c.[1725_1742del];[2171C>T] (p.[G587_G592del];[P724L]) in *WFS1*

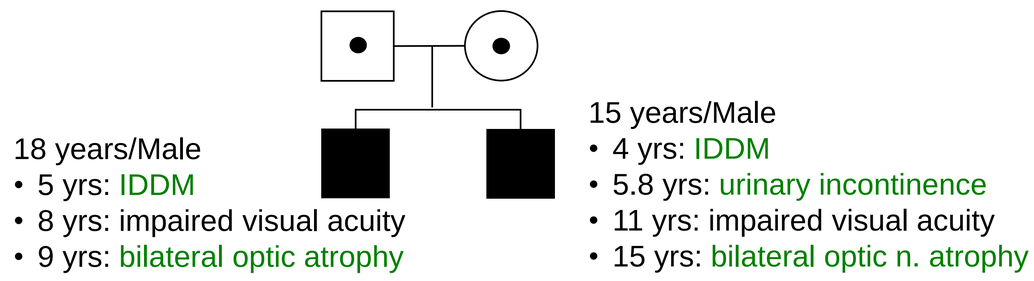
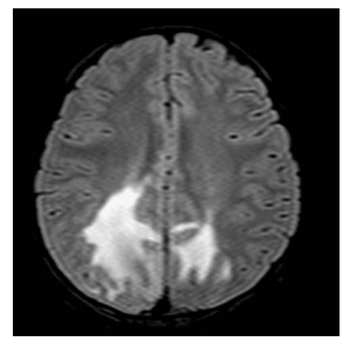


Fig. 3. Pedigree and clinical course of two patients with Wolfram syndrome

A male with IPEX syndrome with unusual clinical features

- Insulin-dependent DM at 11 months of age
- Pure red cell aplasia and membranous glomerulopathy at 39 months of age
- Posterior reversible encephalopathy syndrome (PRES) after a vaccination against influenza A H1N1 virus at age 11 years
- Irregular high signal intensities on the white matters of bilateral posterior frontoparietal lobes
- *FOXP3* gene analysis: c.201+1G>A



An Arab girl with Wolcott-Rallison syndrome

- A 3-month-old Arab girl presented with DM and liver failure, and were diagnosed with Wolcott-Rallison syndrome caused by homozygous mutations in *EIF2AK3* (p.W431*).

Cystic fibrosis-related diabetes (CFRD)

- Two patients with *CFTR* mutations displayed DM with associated features such as chronic pancreatitis and recurrent infections.

Mitochondrial diabetes

- Eight patients with MELAS were classified as mitochondrial DM at age 27.3 ± 11.3 years with the HbA1c level of 6.6 ± 1.8%.

Maturity-onset diabetes of the young (MODY)

- A 12.9 year-old female was diagnosed with MODY3 with mutations in *HNF1A* (p.G292Rfs*26).
- Two patients manifested intrauterine growth retardation, short stature, chronic renal failure, and DM, suggesting MODY5. They were heterozygous for *HNF1B* mutations: p.S148L and p.A166P, respectively.

Conclusions

- It should be considered that diabetic patients who had family history or extra-pancreatic features without β-cell autoantibodies might have monogenic diabetes.
- Molecular diagnosis is important because many of the patients can be treated with a sulfonylurea rather than insulin and influence genetic counseling.
- Identification of the genetic cause of DM is critical to provide appropriate therapeutic options and genetic counselling.

References

1. Hattersley, A., et al., The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes, 2009;10 Suppl 12:33-42.
2. Cho JH et al., DEND syndrome with heterozygous KCNJ11 mutation successfully treated with sulfonylurea. J Korean Med Sci 2017;32:1042-1045

Disclosure statement

The authors have nothing to disclose.