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Invited Review

Genetics for the pediatric endocrinologists - 1

Diagnosis of monogenic diabetes among children and adolescents

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ABSTRACT

The advancement in genetic laboratory technology has helped immensely in the diagnosis of many genetic disorders which could not hitherto be diagnosed. Monogenic diabetes among children and adolescents is not uncommon and needs a high index of clinical suspicion to diagnose. With the availability of genetic diagnostic laboratories with the latest technology, more and more patients should benefit from early diagnosis, specific targeted treatment, and better outcomes. The pediatricians and pediatric endocrinologists managing children with diabetes need to clinically suspect and advise appropriate genetic tests to confirm the diagnosis of monogenic diabetes. Neonatal diabetes mellitus is one of the most rewarding diagnoses, if we pick up a specific genetic abnormality that could respond to sulfonylurea. The child with *KCNJ11* or *ABCC8* gene mutation responding to sulfonylurea could escape from the life-long insulin injections and complications of diabetes. It is equally important to identify other forms of monogenic diabetes as the specific diagnosis can have implications in the treatment, genetic counseling, and identifying other family members harboring the same gene mutation.

Key words: Monogenic diabetes, Maturity-onset diabetes of young, Neonatal diabetes, Glibenclamide

CASE PROFILE

A 6-week-old male baby was brought to the emergency department with rapid breathing, vomiting and an episode of seizure. He was diagnosed with diabetic ketoacidosis (DKA) with the first random blood glucose value of 527 mg/dL. The HbA1c at diagnosis was 10% and fasting C-peptide level was 0.01 ng/mL (normal range: 1.1–4.4 ng/mL). The child was born at term small-for-gestational age (SGA) with a birth weight of 1900 g, by normal vaginal delivery. The antenatal and perinatal periods were uneventful. After successfully managing DKA, the baby was started on treatment with injections of glargine and human regular insulin along with self-monitoring of blood glucose 4–6 times/day. However, the glycemic control remained poor with wide fluctuations of blood glucose.

He was referred to a tertiary care center for the advice of a pediatric endocrinologist. The insulin regimen was continued, and genetic testing was advised to look for genetic mutations in the *KCNJ11* or *ABCC8* genes. These two genes encode the subunits of the ATP-sensitive K^+ (K_{ATP} channel) present in insulin-secreting pancreatic β-cells. A heterozygous disease-causing variant was identified in the *KCNJ11* gene (Location: Exon 1; DNA Description: c.602G>T Protein Description: p. [Arg201Leu]).

He was started on glibenclamide, (an antidiabetic drug that binds to and inhibits the sulfonylurea receptor 1, SUR1 in pancreatic beta cells, and stimulates insulin release) and the clinical response was monitored with frequent blood glucose levels. Over the next 4 weeks, the baby responded to glibenclamide and insulin was slowly tapered off.

During the follow-up, the baby continued to have blood glucose levels below 150 mg/dL with HbA1c below 6.1% and the C-peptide levels of 0.57 ng/mL after 3 months of starting glibenclamide. At the last follow-up at 2.5 years of age, the baby was doing well with normal growth and development for his age. The last HbA1c and C-peptide were 6.0% and 0.90 ng/mL, respectively.

The above case profile highlights the importance of localizing the genetic abnormality in infants with neonatal diabetes mellitus (NDM). The success story of managing this index patient in terms of effective switching to oral sulfonylurea (glibenclamide) from otherwise lifelong insulin injections was made possible only due to the recognition of a specific gene mutation responding to sulfonylurea. This is an example of offering "personalized medicine" to patients with monogenic diabetes and was possible only due to the advances in genetic diagnosis in the recent years. In this short review, we discuss the clinically relevant issues which pediatricians may encounter in day-to-day management of children with suspected monogenic diabetes.

What is Monogenic Diabetes Mellitus?

Monogenic diabetes mellitus is a heterogeneous group of disorders of diabetes caused by mutations in single genes. The mutations primarily affect the pancreatic β-cells leading to reduced insulin secretion. This is in contrast to the polygenic forms of diabetes such as type 1 and type 2 diabetes mellitus which are caused by a number of genes and environmental factors.[1] As of date, 14 different forms of maturity-onset diabetes of the young (MODY) have been recognized.

What are the common forms of monogenic diabetes observed during childhood and adolescence?

The common forms of monogenic diabetes presenting during childhood and adolescence are NDM, MODY, mitochondrial diabetes, and the rare diabetes-associated syndromic diseases [Figure 1].

What are the common forms of monogenic diabetes seen among Indian population?

In India, all the four forms mentioned above, namely, NDM, MODY, mitochondrial diabetes, and diabetes-associated syndromic diseases are seen. Tables 1 and 2 summarize the important published data on the occurrence of different types of monogenic diabetes in India.[2-16]

Are there regional differences in the way monogenic diabetes presents in India?

Regional differences are likely to be there in India in the way the children with monogenic diabetes present to the pediatrician, particularly with regard to the syndromic forms of neonatal diabetes especially in regions where consanguineous marriages are more prevalent, but more data are needed.

When should I suspect monogenic diabetes if a child was initially thought to have type 1 diabetes?

As per the available literature, mostly from the West, around 1–4% of all individuals with diabetes will have one or other form of monogenic diabetes.

The features specific for monogenic diabetes include the following:

1. Diabetes onset before the age of 6 months
2. Diagnosis of diabetes before 30 years of age with the following features:

a) Family history with at least one affected parent with diabetes mellitus and often affecting three generations in the family
b) Significant β-cell reserve is present outside the honeymoon phase (even after 3 years of the diagnosis): C-peptide >300 pmol/L (>0.9 ng/mL)
c) Absence of pancreatic islet autoantibodies such as glutamic acid decarboxylase and zinc transporter, especially at diagnosis
d) Presence of extra-pancreatic dysmorphic features suggesting a specific subtype of monogenic diabetes
e) Non-requirement of insulin to manage diabetes for at least 2 years after the diagnosis
f) Absence of ketosis.

When should I suspect monogenic diabetes if a child was initially diagnosed with type 2 diabetes?

The features specific for monogenic diabetes in children include:

- Not significantly obese and/or the family members who are diabetic are of normal weight
- Acanthosis nigricans is not detected on clinical evaluation
- Ethnic background is from a race with known low occurrence of type 2 diabetes
- There is no evidence of insulin resistance, and the fasting C-peptide levels are within normal range (300–1000 pmol/L or 0.9–3.0 ng/mL)
- Extra-pancreatic dysmorphic features of a specific subtype of monogenic diabetes are present.

What are the different tests or technology available for the genetic diagnosis of monogenic diabetes?

There are two main technologies available for the genetic diagnosis of monogenic diabetes. One is direct gene

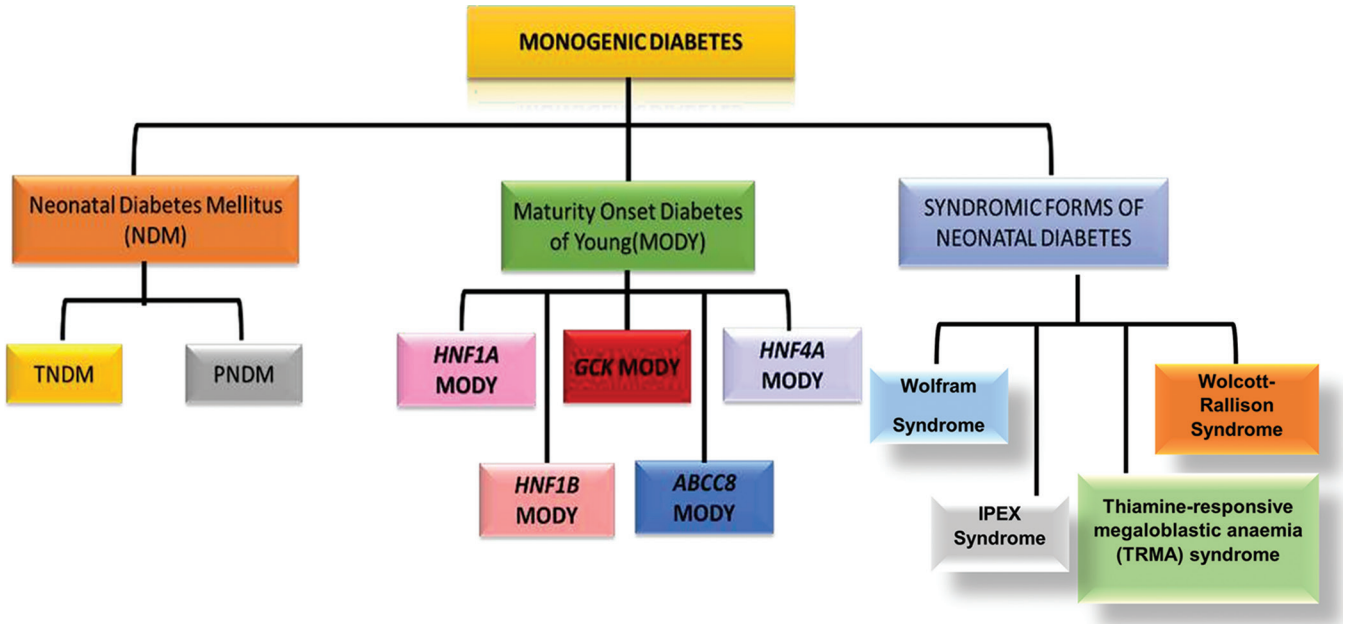

Figure 1: Common types of monogenic diabetes mellitus: NDM: Neonatal diabetes mellitus; TNDM: Transient neonatal diabetes mellitus; PNDM: Permanent neonatal diabetes mellitus; MODY: Maturity onset diabetes of young; IPEX: Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked.

Table 1: Studies reporting frequency of MODY among Indian population.

Author	Study population and age group	Study participants	Gene mutations/syndromes frequency
Mohan *et al*. 1985[2]	<25 years	4560 individuals with diabetes onset <25 years	219 suspected to have MODY (only based on clinical profile)
Radha *et al*. 2009[3]	25±4 years	96 individuals with clinically suspected MODY	HNF-1α mutations accounted for 9 of 96 (9.6%)
Anuradha *et al*. 2011[4]	21±4 years	87 individuals with clinically suspected MODY	3 of 87 (3.4%) subjects had MODY 1 while none of these subjects had *GCK* mutation (MODY 2)
Kanthimathi *et al*. 2014[5]	<18 years	49 individuals with mild hyperglycemia	2 of 49 (4.08%) were found to have *GCK* mutation
Chapla *et al*. 2015[6]	<35 years	56 individuals with clinically diagnosed MODY	11 (19%) positive for mutations in 10 gene panel targeted NGS
Mohan *et al*. 2018[7]	20.85±5.9 years	152 individuals with clinically diagnosed MODY	HNF-1α {MODY 3} - 7.2%; ABCC8 {MODY 12} - 3.3%. Additional variants reported in *AKT2, WFS1, RFX6, NKX6*-1 could be related to MODY.
Lakshmanan *et al*. 2021[8]	Children and adolescents (<18 years)	327 individuals with diabetes	37 (11%) were monogenic diabetes, out of which 15 NDM, 5 MODY, 13 Wolfram syndrome, 2 H-Syndrome, 1 Mitochondrial DM, 1 TRMA

MODY: Maturity Onset Diabetes of Young, DM: Diabetes mellitus, NDM: Neonatal diabetes mellitus, TRMA: Thiamine-responsive megaloblastic anemia, GCK: Glucokinase, NGS: Next generation sequencing

sequencing by Sanger method and the other is high throughput next generation sequencing (NGS). In Sanger method, sequencing is done typically of one gene at a time choosing the most relevant genes for monogenic diabetes. This is very time-consuming, laborious, and cost-intensive. NGS includes targeted sequencing (tNGS) using gene panels, whole exome sequencing (WES), and whole genome sequencing (WGS).

These days, tNGS using gene panels of relevant genes is preferred over Sanger sequencing. This method facilitates

Table 2: Studies reporting NDM among Indian population.

Author	Study Population	Region/City	Gene Mutations/Syndromes frequency
Varadarajan 2013[9]	40 Infants with DM 29 tested for genetic mutations	Chennai	Wolcott-Rallison syndrome (*EIF2AK3*) - 9 Berardinelli-Seip lipodystrophy - 1 Fanconi-Bickel syndrome -1 *ABCC8* gene mutation - 5 *KCNJ11* gene mutation - 2 *GCK* gene mutation - 1 *INS1* gene mutation - 1
Jahnavi *et al*. 2014[10]	33 subjects with infantile-onset DM	Chennai	*ABCC8* - 7 *KCNJ11* - 3 *INS* gene mutation - 2 Berardinelli-Seip syndrome (*AGPAT2*) - 1 Fanconi-Bickel syndrome (*SLC2A2*) - 1
Ganesh *et al*. 2016[11]	10 children with NDM (onset <6 months)	Chennai	**Transient NDM - 1** Chromosome 6q24 **Permanent NDM - 9** *KCNJ11* gene mutation - 1 *ABCC8* gene mutation - 2 *INS* gene mutation - 2 *EIF2AK3* gene mutation - 1 *PDX1* gene mutation -1 *SLC19A2* gene mutation - 1 *NEUROD1* gene mutation - 1
Jain *et al*. 2017[12]	11 infants with NDM 9 tested for genetic mutations	New Delhi	**Permanent NDM - 8** *KCNJ11* gene mutation - 3 *ABCC8* gene mutation - 1 *INS* gene mutation- 1 **Transient NDM - 1** *ZFP57* gene mutation - 1
Kumar *et al*. 2019[13]	34 subjects with infantile-onset DM 29 children underwent genetic testing	Chandigarh	**Permanent NDM - 9** *KCNJ11* gene mutation - 7 (5 out of 7 switched to sulfonylurea) Wolcott–Rallison syndrome (*EIF2AK3*) - 1 Homozygous *GCK* mutation - 1 **Transient NDM - 3** *KCNJ11* gene mutation - 2 *ABCC8* gene mutation - 1
Gopi *et al*. 2021[14]	181 children with permanent NDM	Chennai	**Permanent NDM** *KCNJ11* gene mutation - 20 (DEND Syndrome in 3/20) *ABCC8* gene mutation - 19 33 out of total 39 (84%) patients (*KCNJ11+ABCC8*) switched to sulfonylurea
Nayak *et al*. 2021[15]	12 infants with NDM 8 presented at <6 months	Lucknow	**Transient NDM - 3** *KCNJ11* gene mutation - 1 *INS* gene mutation- 1 *ABCC8* gene mutation- 1 **Permanent NDM - 7** Homozygous *GCK* gene mutation - 2 (siblings) *TRMA* gene mutation - 2 (siblings) IPEX syndrome -1 Wolcott-Rallison syndrome - 2
Gopi *et al*. 2021[16]	189 children with permanent NDM	Chennai	**Permanent NDM** 9 *INS* gene mutations in 8 children

DM: Diabetes mellitus, NDM: Neonatal diabetes mellitus

the investigation of a large number of genes at the same time, making it rapid and economical. However, when a mutation is detected in a gene through this method, we validate for just that particular mutation using Sanger method as this serves as a gold standard.

In general, gene panels will be the appropriate test to order for monogenic diabetes, but there are cases where the clinical features clearly fit with a mutation of a distinct gene, as in syndromes of monogenic diabetes. In such cases, it is enough to do Sanger sequencing of the specific relevant genes in question.

WES or WGS are generally performed as gene discovery methods for detecting novel genes. They are high throughput and labor-intensive because of the volume of data that are generated.

At the Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialties Centre, we have set up a separate department of "Monogenic Diabetes." This is a first such department in India. In our laboratory, we perform genetic testing for all the known and relevant genes for monogenic diabetes. The genetic testing for neonatal diabetes and syndromes of NDM is done free of cost by us. (Websites: www.mdrf.in; www.monogenicdiabetes.in).

How can we improve the diagnosis of monogenic diabetes in India?

First, it is important to correctly identify the genetic cause of monogenic diabetes since it has implications for treatment, surveillance of complications, associated extra-pancreatic disorders, and identification of affected and at-risk family members.[17] Each genetic subtype of monogenic diabetes demands different management and treatment and entails proper interpretation of pathogenicity. A strategy to perform differential diagnosis of monogenic diabetes is presented in [Figure 2].

Another important aspect is raising the awareness of monogenic diabetes and making the diagnosis more accessible, which will certainly improve disease prognosis and management in affected children and their families.[18]

Should parents and unaffected siblings be tested?

This is a very important aspect in genetic studies. Genetics studies talk about the inheritance pattern of the mutations and testing the parents will add information regarding from whom the mutation was inherited and whether the mutation co-segregates with the disease. In addition, testing of the unaffected children enhances the predictive ability and will provide the information about the at-risk status of the siblings. This kind of testing is called *cascade testing*.

Are there any recent advances in diagnosis and management for the pediatrician?

The field of diabetes genetics has advanced so much that it is now possible to deliver on precision medicine. Assessing whether the identified variation in a gene is truly disease-causing or clinically actionable has been a big challenge for the molecular geneticist. However, these are being done now and they are the recent advances in this field.

How should you manage specific subtypes of monogenic diabetes?

Many of the common forms of monogenic diabetes have specific management strategies. These are based on specific mutations in the genes, leading to precision treatment. Therefore, the treatment is based on genetic etiology.

The common gene mutations responsible for NDM are in *KCNJ11, ABCC8, INS,* and 6q24 region.[19] NDM could be transient (45%), permanent (45%), and syndromic (10%). However, the relative frequency of the three forms of NDM is different in the Indian studies with transient <10–20%, permanent 60–70%, and syndromic NDM 20–50%. The Indian studies reporting neonatal diabetes are summarized in Table 2.[9-16] The different forms of neonatal diabetes are listed in Box 1.

Mutations in *KCNJ11* and *ABCC8* genes (which encode the 2 subunits of K_{ATP} channel, KIR6.2, and SUR, respectively) lead to NDM and can manifest as transient (TNDM) or permanent (PNDM) forms. In general, TNDM have an average onset at 4 weeks and undergoes remission by around 36 weeks and has high chances of relapse later in life. The salient features of TNDM and PNDM are listed in Box 2.

PNDM manifests around first week of life and remains life-long. Although to bring the glucose down, insulin is administered as soon as a clinical diagnosis is made, genetic testing may reveal K_{ATP} related neonatal diabetes, and then patient can be shifted to sulfonylureas (SU). Since the KIR6.2 channels are also present in the brain neurons, SU drugs also help improve neurodevelopmental problems including seizures, a common feature of these mutations, and in achieving excellent glycemic control.

6q24-related TNDM is more severe than the K_{ATP}-related TNDM with severe restriction of intrauterine growth and early onset of diabetes, but likely to have earlier remission. Affected individuals can have macroglossia and/or umbilical hernia. Insulin is the only treatment option, as these children do not respond to sulfonylurea.

In TNDM, the need for insulin gradually declines and remission is achieved at an average of 4–12 months; relapse occurs very often usually in adolescence, pregnancy, or adulthood. This is the remitting-relapsing diabetes. The

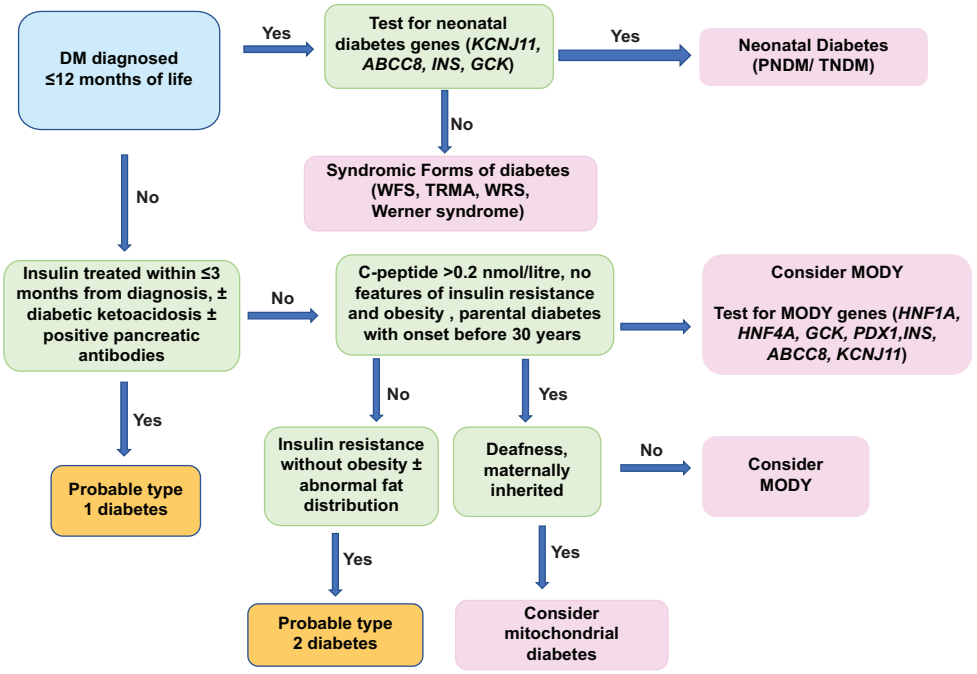

Figure 2: Strategy for differential diagnosis of monogenic diabetes mellitus. NDM: Neonatal diabetes mellitus, TNDM: Transient neonatal diabetes mellitus, PNDM: Permanent neonatal diabetes mellitus, MODY: Maturity onset diabetes of young, IPEX: Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked, WFS: Wolfram Syndrome, TRMA: Thiamine-responsive megaloblastic anemia, WRS: Wolcott Rallison Syndrome.

Box 1: Common forms of transient and permanent NDM.

Subtype	Relative frequency	Common genes affected	Specific phenotype
Transient NDM			
TNDM1 6q24 related	70%	*PLAGL, HYMAI*	Umbilical hernia, macroglossia
TNDM2	15%	*KCNJ11*	Developmental delay
	10%	*ABCC8*	Developmental delay
	5%	*INS, HNF-1B,*	Pancreatic hypoplasia, renal abnormalities (*HNF-1B*)
		SLCA2A	Rickets, round facies, mild hyperglycemia (*SLCA2A*)
Permanent NDM			
	50%	*KCNJ11*	± DEND syndrome
	30%	*INS*	No dysmorphism
	15%	*ABCC8*	± DEND syndrome
	3%	*GCK*-homozygous	No dysmorphism
	2%	*PDX-1, HNF-1B* homozygous	Pancreatic hypoplasia and renal abnormalities (*HNF-1B*)

NDM: Neonatal diabetes mellitus

Box 2: Clinical differences between transient and permanent NDM.

Transient NDM	Permanent NDM
• Earlier age at onset (<1 month)	• Onset usually >1 month
• IUGR: more frequent/severe	• Less severe IUGR
• Less initial insulin requirement	• Higher insulin requirement
• Less frequency of DKA	• Higher rates of developing DKA

DKA: Diabetic ketoacidosis, IUGR: Intrauterine growth restriction, NDM: Neonatal diabetes mellitus, DKA: Diabetic ketoacidosis

relapsed diabetes usually responds to sulfonylurea and/or dipeptidyl peptidase-4 (DPP-4) inhibitors, insulin therapy may not be required.

In those children with PNDM having *INS* mutations, insulin is the only treatment. A few forms of PNDM are a part of complex syndromes, having multisystemic extra-pancreatic manifestations. Wolcott-Rallison syndrome is one of the common syndromic forms of NDM seen in India and in populations with high consanguinity. Common syndromes

and the associated genetic mutations presenting with NDM are listed in Box 3.

In the case of MODY, treatment and management strategies are dependent on the subtype of MODY.[7] This is detailed below.

HNF1A-MODY (MODY 3): This is the most common form of MODY in India and in many parts of the world.[3] It is characterized by progressive β-cell loss, and progressive loss of insulin secretion, with diabetes onset during adolescence or early adulthood. The first-line treatment is low dose sulfonylurea, which will partly bypass the defective insulin secretory response. Some individuals with *HNF1A*-MODY can be very sensitive to sulfonylurea and experience hypoglycemia even on very small doses. Glucagon-like peptide-1 agonists and DPP-4 inhibitors have been shown to be efficacious and may be useful as adjunctive therapy when glycemic control is inadequate with sulfonylurea monotherapy.

Box 3: Common syndromic forms of NDM and their characteristic phenotypes.

Genes affected	Specific phenotype
EIF2AK3	Spondyloepiphyseal dysplasia, renal anomalies, liver failure, neutropenia, intellectual disability, and hypothyroidism (Wolcott-Rallison syndrome)
FOXP3	IPEX syndrome presenting as hypothyroidism, diarrhea and eczema
GLIS3	Hypothyroidism, hepatic fibrosis, glaucoma, cystic kidneys, and developmental delay
PTF1A	Pancreatic and cerebellum agenesis, and microcephaly
RFX6	Pancreatic hypoplasia, and digestive system defects (Mitchell-Riley syndrome)
NEUROG3	Congenital malabsorptive diarrhea and enteroendocrine cell dysgenesis
GATA6	Pancreatic agenesis and cardiac malformations
MNX1	Developmental delay, neurogenic bladder, sacral agenesis, and imperforate anus
NKX2	Developmental delay, hypotonia, hearing impairment, cortical blindness, and short stature
NEUROD1	Cerebellar hypoplasia, sensorineural deafness, and visual impairment
PAX 6	Central nervous system phenotype – microcephaly and panhypopituitarism Ocular phenotype – aniridia, keratopathy, optic nerve defects, cataracts, microphthalmia, and anophthalmia
SLC19A2	Recessive mutations lead to NDM, TRMA and deafness with or without cardiac manifestations (Rogers syndrome)
SLC2A2	DM with hepatomegaly, glycosuria, proteinuria, hypophosphatemic rickets (Fanconi–Bickel syndrome)
WFS1	DIDMOAD or Wolfram Syndrome

IPEX: Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked, NDM: Neonatal diabetes mellitus, TRMA: Thiamine-responsive megaloblastic anemia, DIDMOAD: Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness

HNF4A-MODY (MODY 1): The treatment modality is the same as *HNF1A*-MODY.

HNF1B-MODY (MODY 5): Heterozygous mutations in *HNF1B* gene presents with heterogeneous phenotypes which include developmental cystic kidney disease alone, diabetes alone, or a combination of both. This type of MODY is not sensitive to SU, requiring insulin therapy.

GCK-MODY (MODY 2): This form is distinctive from other MODY types and is characterized by mild hyperglycemia due to an increased threshold for glucose-induced insulin release. It does not require pharmacologic treatment apart from pregnancy in woman with *GCK*-MODY. In pregnancy, appropriate management is predicted based on the genotype of the fetus. If the fetus inherits *GCK* mutations, mildly elevated maternal glucose levels are sensed as normal by the fetus and treatment is not required. On the other hand, if the fetus does not carry the mutations, mildly elevated maternal glucose will induce increased insulin secretion by the fetus which can lead to microsomia. In such cases, insulin therapy must be considered.

CONCLUSION

In a nutshell, gene-based precision treatment for monogenic diabetes has already arrived in the clinical setting. Pediatricians and pediatric endocrinologists managing children with diabetes need to be aware of when to suspect monogenic diabetes in a given child with diabetes. The confirmation of genetic diagnosis has implications in the treatment, genetic counseling, and identifying other family members harboring the same gene mutation.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Radha V, Mohan V. Genetic basis of monogenic diabetes. Curr Sci 2017;113:1277.

2. Mohan V, Ramachandran A, Snehalatha C, Mohan R, Bharani G, Viswanathan M. High prevalence of maturity-onset diabetes of the young (MODY) among Indians. Diabetes Care 1985;8:371-4.
3. Radha V, Ek J, Anuradha S, Hansen T, Pedersen O, Mohan V. Identification of novel variants in the hepatocyte nuclear factor-1alpha gene in South Indian patients with maturity onset diabetes of young. J Clin Endocrinol Metab 2009;94:1959-65.
4. Anuradha S, Radha V, Mohan V. Association of novel variants in the hepatocyte nuclear factor 4A gene with maturity onset diabetes of the young and early onset type 2 diabetes. Clin Genet 2011;80:541-9.
5. Kanthimathi S, Jahnavi S, Balamurugan K, Ranjani H, Sonya J, Goswami S, *et al*. Glucokinase gene mutations (MODY 2) in Asian Indians. Diabetes Technol Ther 2014;16:180-5.
6. Chapla A, Mruthyunjaya MD, Asha HS, Varghese D, Varshney M, Vasan SK, *et al*. Maturity onset diabetes of the young in India a distinctive mutation pattern identified through targeted next-generation sequencing. Clin Endocrinol (Oxf) 2015;82:533-42.
7. Mohan V, Radha V, Nguyen TT, Stawiski EW, Pahuja KB, Goldstein LD, *et al*. Comprehensive genomic analysis identifies pathogenic variants in maturity-onset diabetes of the young (MODY) patients in South India. BMC Med Genet 2018;19:22.
8. Lakshmanan NK, Pavithran PV, Bhavani N, Abraham N, Kumar H, Nair V, *et al*. Monogenic diabetes: A single center experience from South India. Pediatr Diabetes 2021;22:75-81.
9. Varadarajan P. Infantile onset diabetes mellitus in developing countries India. World J Diabetes 2016;7:134-41.
10. Jahnavi S, Poovazhagi V, Mohan V, Bodhini D, Raghupathy P, Amutha A, *et al*. Clinical and molecular characterization of neonatal diabetes and monogenic syndromic diabetes in Asian Indian children. Clin Genet 2013;83:439-45.
11. Ganesh R, Suresh N, Vasanthi T, Ravikumar KG. Neonatal diabetes: A case series. Indian Pediatr 2017;54:33-6.
12. Jain V, Satapathy A, Yadav J, Sharma R, Radha V, Mohan V, *et al*. Clinical and molecular characterization of children with neonatal diabetes mellitus at a tertiary care center in Northern India. Indian Pediatr 2017;54:467-71.
13. Kumar R, Pilania RK, Verma D, Yadav J, Dayal D. Infantile Onset Diabetes Mellitus: Fifteen Years' Experience from a Tertiary Care Pediatric Center in North India. Annual Meeting of Sri Lanka College of Endocrinologists, Colombo, Sri Lanka, August 1-3, 2019: Abstracts. Sri Lanka Journal of Diabetes Endocrinology Metabolism; 2019. Available from: https://www.researchgate.net/publication/341399444 [Last accessed on 2022 Mar 03].
14. Gopi S, Kavitha B, Kanthimathi S, Kannan A, Kumar R, Joshi R, *et al*. Genotype-phenotype correlation of K_{ATP} channel gene defects causing permanent neonatal diabetes in Indian patients. Pediatr Diabetes 2021;22:82-92.
15. Nayak S, Sarangi AN, Sahoo SK, Mangla P, Tripathy M, Rao S, *et al*. Neonatal diabetes mellitus: Novel mutations. Indian J Pediatr 2021;88:785-92.
16. Gopi S, Gowri P, Panda JK, Sathyanarayana SO, Gupta S, Chandru S, *et al*. Insulin gene mutations linked to permanent neonatal diabetes mellitus in Indian population. J Diabetes Complications 2021;35:108022.
17. Owen K. Diagnosing monogenic diabetes in clinical practice. Pract Diabetes 2017;34:205-9.
18. Owen K, Shepherd M, Stride A, Ellard S, Hattersley A. Heterogeneity in young adult-onset diabetes: Aetiology alters clinical characteristics. Diabetic Med 2002;19:758-61.
19. De Franco E, Flanagan S, Houghton J, Allen H, Mackay D, Temple I, *et al*. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: An international cohort study. Lancet 2015;386:957-63.

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