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EDITORIAL

Monogenic diabetes—diagnostic conundrums

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Diabetes mellitus (DM) is a global pandemic [1] that affects nearly 382 million people worldwide [2]. The vast majority of patients (approximately 85 %) are classified into polygenic type 1 diabetes (T1D) or type 2 diabetes (T2D). However, with growing evidence from genomic research, several monogenic causes of diabetes have emerged. Monogenic forms of diabetes include maturity onset of diabetes of young (MODY), neonatal diabetes and rare syndromic forms of diabetes [3].

Maturity onset of diabetes of young

Mutations involving 13 different genes have been reported to cause MODY and more than 20 genes have been reported to be implicated in neonatal diabetes and rare syndromic forms of diabetes [3]. However, till recently, the molecular diagnosis of these monogenic disorders included sequential screening of only a few related genes based on the phenotype [4]. Moreover, due to the prohibitive cost and limitations associated with the scalability of Sanger sequencing, most diagnostic laboratories screen for hepatocyte nuclear factor 1alpha (*HNF1A*), glucokinase (*GCK*) and hepatocyte nuclear factor 4 alpha (*HNF4A*) mutations in MODY [5] or the ATP-sensitive potassium channels, KCNJ11 and ABCC8, and the insulin gene (INS) mutations in neonatal diabetes [3]. Only a few of those patients who test negative for mutations in these genes are subjected to further genetic testing of the less common monogenic forms of diabetes [4]. In developing countries, due to a paucity of clinician-related awareness, limited genetic diagnostic facilities and affordability, patients with diabetes are often misdiagnosed as T1D or T2D and may potentially receive inappropriate therapy [6]. Furthermore, with the overlapping clinical features with common forms of polygenic diabetes, the diagnosis of monogenic diabetes becomes challenging [7].

Neonatal diabetes mellitus

Neonatal diabetes mellitus (NDM) is a rare monogenic form of diabetes that occurs within 6 months of infancy. The incidence of NDM is 1 in 500,000 live births. Most of these infants are misdiagnosed as having type 1 diabetes mellitus and have been advised long-term insulin. The major difference between NDM and type 1 diabetes is the age of onset of the disease. Usually T1DM occurs after the first 6 months of life owing to increased activation of the immune system which occurs after 6 months. There are two types of NMD, permanent neonatal diabetes mellitus (PNDM) wherein the disease is lifelong and transient neonatal diabetes mellitus (TNDM) in which the diabetes disappears during infancy but can reappear later in life [8, 9].

The clinical symptoms of NDM include frequent micturition, dehydration and failure to thrive. These symptoms mimic those of distal or proximal renal tubular acidosis of congenital origin. However, the major differentiating feature between NDM and renal tubular dysfunction is the elevated level of plasma glucose in NDM. Some infants may present with frank diabetic ketoacidosis. A small for gestational-age baby may be associated with NDM due to the presence of insulinopenia. Following delivery, these babies fail to gain weight when

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compared to the infants of the same age and sex. Appropriate therapy (insulin initially, then followed by sulphonylurea agents) improves and may normalize the growth and development of the infant. Therefore, genetic screening may help in confirming the diagnosis of these disorders and potentially evading long-term insulin therapy [8, 9].

NDM is a true monogenic condition where hyperglycaemia is related to a single-gene mutation [8]. Recently, Al-Agha et al. from Saudi Arabia has performed NDM gene screening in eight children with hyperglycaemia diagnosed during 1 to 17 weeks of birth. Initial screening revealed one patient with a KCNJ11 mutation and one with an insulin gene mutation. Furthermore, screening of ABCC8 and FOXP3 did not reveal any mutations, therefore yielding a mutation-positive rate of 25 % when screened for specific genes in patients with permanent NDM [9]. Another study from China performed by Huang et.al. screened four cases of PNDM for mutations in ABCC8, KCNJ11 and INS. However, they could not find any causative mutations and therefore could not provide a definitive diagnosis [10]. Therefore, in the developing countries, various mutation screening studies yielded 0–33 % mutation-positive rates when screened for 3 to 4 genes (ABCC8, KCNJ11, INS and FOXP3) [11]. However, the rarer forms of known ND genes further need to be tested to increase the likelihood of making a confirmed genetic diagnosis.

Recent studies utilizing next-generation sequencing (NGS)-based parallel multi-gene testing have shown promising results [3, 5], and the testing has been proven to find the genetic cause even with limited phenotypic information and also in the absence of characteristic features in monogenic diabetes-related subtypes [12]. Further, with the identification of digenic mutations in MODY [5] and also often with overlapping clinical features [7], project the need for parallel multigene testing in monogenic diabetes which could provide a comprehensive genetic portrait.

Wolfram syndrome

Wolfram or DIDMOAD is an uncommon disorder which has been considered as a differential diagnosis in young patient with diabetes mellitus. The clinical diagnosis of Wolfram syndrome can be clenched if routine funduscopy is practiced in all patients with young onset diabetes mellitus. DIDMOAD stands for diabetes insipidus, diabetes mellitus, optic atrophy and deafness. The temporal profile of this disorder is that diabetes mellitus presents around the age of 6 years followed by optic atrophy at around 11 years. Most patients will have loss of vision after 8 to 10 years after signs of optic atrophy first begin. Around three fourths of patients effected by Wolfram syndrome will have diabetes insipidus and sensory neural deafness. Moreover, up to 90 percent of these patients can have various urinary tract problems ranging from bladder outlet obstruction to an atonic bladder [13].

In case of syndromic forms of diabetes, phenotype guided specific gene sequencing could be adopted. A study published by Abbasi et al. have studied two Iranian patients with Wolfram syndrome which is a rare neurodegenerative disorder [14]. Wolfram syndrome (WFS1) gene has eight exons and screening of only the eighth exon in two patients revealed a pathogenic variant providing a confirmed diagnosis [14]. However, in case of variable expression of this gene, it is important to note that there could be heterozygote carriers [15] or the mutation could be present in other exons of WFS1 or in WFS2 gene in which few mutations have been reported. Till date, there are around 230 WFS1 gene mutations that have been reported; however, there is a poor understanding of the relationship between the non-synonymous coding variants and the phenotype. Therefore, studies looking at short fragments or partial gene require extensive bioinformatics predication and careful interpretation of the novel variants identified [16].

Even with a considerable phenotypic heterogeneity in monogenic diabetes [3], a confirmed genetic diagnosis may help in understanding molecular cause for diabetes and also help in cases where there is significant change in medical management. Patients' families could benefit through genetic counselling and also to predict their clinical course and familial risk. Therefore, a heterogeneous disorder like MODY or neonatal diabetes would require NGS-based multi-gene testing to uncover the molecular basis and pave a way to personalized genetic medicine through improved glycaemic control and quality of life.

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