ATYPICAL DIABETES: LADA, MODY AND TYPE 3 DIABETES - AN EVIDENCE BASED REVIEW

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Abstract

Type 1 and Type 2 Diabetes Mellitus are the most common forms of Diabetes. This review article focuses on the other uncommon types of diabetes like LADA, MODY and Type 3 Diabetes. MODY is a monogenic form of diabetes, in contrast to polygenic diabetes (Type 1 DM and Type 2DM) monogenic diabetes are caused by defect in a single gene. Latent Autoimmune Diabetes in Adults (LADA) is an adult-onset autoimmune diabetes, in which the failure of autoimmune β-cell failure happens slowly compared to type 1 DM. The Type 3 Diabetes is a neuroendocrine disorder which is characterized by chronic insulin resistance with insulin deficiency in brain. This type of diabetes represents the progression of type 2 diabetes to Alzheimer's disease and thus plays a major pathogenesis in the neuro- degeneration of Alzheimer's disease. Thus, this review is aimed to provide further information about atypical diabetes.

Keywords: LADA, MODY, Type 3 Diabetes, Atypical Diabetes, Alzheimer's disease

Introduction

Diabetes, a metabolic disorder, is greatly influenced by the genetics. Thus, the diagnosis of diabetes should not be restricted to type 1 and type 2. Genotypic and Phenotypic characters also play a major role in the diagnosis of diabetes (1). Considering the molecular changes, other newer forms of diabetes such as LADA, MODY and Type 3 Diabetes should also be taken for diagnosing in general practicing. Optimized treatment can be provided only with accurate prognosis. Failure in this can lead to several complications

such as hemochromatosis (2). Each patient is different from another and treatment should be personalized based on the type of diabetes. There is a need for considering the personalized medicine and precision heath (3). The concept of precision medicine ensures enhanced therapeutic efficacy and safer treatment which decreases the disease burden (4). Thus the aim of our article is to provide a consolidated write up on these atypical forms of diabetes.

Materials and Methods

A thorough literature review was done using the available databases such as PubMed, Science Direct, PLOS using the keywords as LADA, MODY, Type 3 diabetes mellitus. The studies were critically reviewed, and the following discussions were drafted.

Results and Discussion

Maturity - Onset Diabetes of the Young: The term Maturity – Onset Diabetes of the Young (MODY) was first used at the Fifth Congress of the International Diabetes Federation held at Toronto in 1964 (5). The prevalence of MODY is too less that it accounts for just 1-2% in developed countries. Misdiagnosing as Type 1 and Type 2 is the main reason for its lesser prevalence. An example from UK, where 80% of the MODY patients misdiagnosed as Type 1 or 2 Diabetes clearly projects this (6). In contrast to polygenic diabetes (Type 1DM and Type 2DM) monogenic diabetes (MODY) are caused by defect in a single gene (7,8). It can be suspected in patients with a family history of Type 2 DM for 2 or more generation and a pattern of autosomal–dominant inheritance. MODY is most commonly seen in adolescents and young adults under the age of 25. Since the clinical features of MODY are almost same as that of the Type 1 DM and Type 2 DM, most often this is misdiagnosed. Thus a molecular diagnosis is essential for the early detection to optimize treatment (9). There are 14 different subtypes of MODY (8) each caused by defect in the corresponding specific gene: HNF4α-MODY (MODY1), GCK-MODY (MODY2), HNF1α-MODY (MODY3), PDX1/IPF1-MODY (MODY4), HNF-1β-MODY (MODY5), NEUROD1-MODY (MODY6), KLF11-MODY (MODY7), CEL-MODY (MODY8), PAX4-MODY (MODY9), INS- MODY (MODY10), BLK-MODY (MODY11), ABCC8-MODY (MODY12), KCNJ11-MODY (MODY13) and APPL1-MODY (MODY14) **.**The gene corresponding to each type of MODY and its effect upon mutation is mentioned in Table 1 (6).

Table 1: Different Types of Mody with its Responsible Genes and its Mutagenic Effect

TYPE	GENES	EFFECT
MODY 1	HNF4α (Hepatic nuclear factor 4 alpha)	Decrease Insulin production
MODY 2	GCK (Glucokinase enzyme)	Increase insulin secretion Alter glucose threshold Increase fasting blood sugar
MODY 3	HNF1α (Hepatocyte nuclear factor 1 alpha)	Increase β-cell apoptosis
MODY 4	PDX1/IPF1(Pancreatic anduodenal homeobox 1 /insulin promoter factor 1)	Pancreatic anomaly
MODY 5	HNF-1β (Hepatocyte nuclear factor-1β)	Impaired glucose metabolism

MODY 6	NEUROD1(Neurogenic differentiation-1)	Autosomal dominant inheritance mutation
MODY 7	KLF11(Krueppel-like factor 11)	Impaired β-cells function
MODY 8	CEL (Carboxyl-ester lipase)	Impaired exocrine &endocrine functioning of pancreas
MODY 9	PAX4 (Paired box gene 4)	Inhibit β-cell proliferation
MODY 10	INS (Insulin gene)	Defect in NF-κB (nuclear factor kappa-light-chain- enhancer of activated B cells)
MODY 11	BLK (Lymphocyte kinase tyrosine kinase)	Affects MIN6 B-cells (a highly differentiated B- cell line)
MODY 12	ABCC8 (ATP-binding cassette transporter subfamily C member 8)	Congenital hyperinsulinism-due to inactivating mutation permanent or transient neonatal diabetes- due to activating mutation
MODY 13	KCNJ11 (The potassium channel, rectifying subfamily J, having member 11)	Channel inactivation that cause hyperinsulinism
MODY 14	APPL1 (Adapter protein, phosphotyrosine interaction domain and leucine zipper containing protein-1)	Apoptosis and over expression causing dysmorphic phenotypes

The most common form of MODY is the mutation in the gene HNF1A and GCK, whereas the prevalence of HNF4A is 5-10% of MODY. The mutation in the gene IPF 1 and CEL is the most rarest of MODY(9). Clinical characteristics of GCK-MODY (MODY 2) include mild fasting hyperglycemia throughout their life and small incremental glucose rise after carbohydrate intake.HNF1 B- MODY is often characterized with malformations of the genitourinary tract, pancreatic atrophy and exocrine insufficiency. INS, KNJ11, ABCC8 are mostly associated with neonatal diabetes (9). The main etiology for MODY 2 is the mutations in Glucokinase (GCK) gene and for MODY3 and MODY 1 is the mutation in hepatocyte nuclear factor (HNF)1A/4A genes (7). Elevated blood glucose levels trigger the activation of glucokinase enzyme which releases insulin from β cells (8). A defect in this enzyme will lead to inadequate response to elevated blood glucose level. The mutation in GCK gene results in mild, asymptomatic and stable fasting hyperglycemia and thus does not require any specific treatment. Whereas the mutation in HNF1A and HNF4A will lead to a progressive β – cell dysfunction of pancreas that results in hyperglycemia which will further lead to microvascular complications. A mutation in the HNF1B will result in MODY5, which is characterized by pancreatic agenesis, renal abnormalities, genital tract malformations and liver dysfunction (7). Once a person has been diagnosed with any type of MODY, screening procedures such as hemoglobin A1C, fasting plasma glucose, 2-h post glucose levels, 1-h post glucose levels and OGTT should be recommended in all family member irrespective of having diabetes (5). Benjamin J Wheeler et al (10) have reported the prevalence of MODY among the Caucasian population with its clinical manifestation three

case presentations of MODY diabetes boy, a 9-year-old Caucasian boy, a 14 year old Cook Island Maori girl and a 11 year old Caucasian girl (10). Patients with HNF1A- MODY has low renal threshold for glycosuria and marked sensitivity to sulfonylureas. In the initial phase of MODY, sulfonylureas are effective, and insulin may be required in the later stages (9). A study conducted among 12 Brazilian families having autosomal-dominant early-onset type 2 diabetes showed a prevalence of approximately 42% for MODY diabetes (11).

Latent Autoimmune Diabetes in Adults: Latent Autoimmune Diabetes in Adults (LADA) is a prevalent form of autoimmune diabetes (12). The history of LADA started from 1986, when Groop et al (13) observed a group of Type 2 diabetic patients with preserved β-cell function despite of having islet auto antibodies. The features of this diabetes were clearly different from type 1 and type 2 DM and they referred this as latent Type 1 diabetes. Later, it was Tuomi et al. and Zimmet et al coined the term LADA for this autoimmune diabetes. Recently, two new terms "LADY-like" (Latent Autoimmune Diabetes in the Young) and LADAC (Latent Autoimmune Diabetes in Children) was introduced based on the diagnosis of islets antibodies without insulin dependency in two children (14). Latent Autoimmune Diabetes in Adults (LADA) is an adult-onset autoimmune diabetes, in which the failure of autoimmune β-cell failure is a slow process(14,15). Hence the usage of insulin is not necessary during the first few months of the disease.25% of type 2 DM patients below the age of 35 have LADA, whereas only 10% of Type 2 DM patients above 35 years develop LADA(13). LADA is often misdiagnosed as type 2 diabetes mellitus (15). Males are found to be more prone to LADA than females (16). LADA patients having multiple islet antibodies when compared to those having only GAD antibodies or Islet Cell antibodies have a greater chance of developing complete β-cell failure within 5 years. As the concentration of Islet antibodies are high, the β-cell function is found to be declined (14). The frequency that a LADA patient gets preclinical carotid atherosclerosis was found to be comparable or even higher while compared to that of type 1 and type 2 Diabetic patients (16). A comparative study on the response of C- peptide to Mixed Meal Tolerance Test in type 2 diabetes mellitus, adult onset type 1 diabetes mellitus and LADA patients with different disease duration shows an intermediate response LADA patients to C-peptide while compared to type 1 and 2 diabetes mellitus (11). Diagnosis of LADA is mainly determined by considering age of onset of the disease in >30 years, presence of high titers in anti-islet antibodies and non-requirement of insulin therapy during the first few years of diagnosis. Confirmatory diagnosis requires the determination of GAD autoantibodies and C- peptide levels (17). Even though insulin therapy is the preferred choice for LADA, obese patients are also found to be effective with metformin (12). The use of infliximab was also found to be effective in LADA. A randomized, placebo controlled, double- blind study on diabetic patients supports the usage of Disease Modifying Antirheumatic Drugs (DMARDs) for LADA (18). Administration of Vitamin D in LADA patients help in delaying the progression of the disease. Also, LADA patients treated with Sitagliptin was found to have a longer insulin- free period. Sitagliptin is a DPP-4 inhibitor which slows the progression of β cell function (14). Table 2 depicts the comparison of LADA and MODY.

Table 2: LADA vs MODY

Characteristics	MODY	LADA
Etiology	Mutation in a single gene	Auto immune destruction of pancreatic beta- cell
Drug of Choice	Insulin is the drug of choice	Insulin is the drug of choice
Other treatment	Sulfonylurea	Metformin, Infliximab, DMARDs, Sitagliptin
Islet cell antibodies	Absent	Present

Type 3 Diabetes Mellitus: Type 3 Diabetes is a neuroendocrine disorder characterized by chronic insulin resistance with insulin deficiency in brain (19). This type of diabetes represents the progression of type 2 diabetes to Alzheimer's disease and thus plays a major pathogenesis in the neurodegeneration of Alzheimer's disease (20). Insulin Degrading Enzyme (IDE) plays a major role in this conversion by altering several metabolic pathways. Insulin signaling pathways present in the several cells plays a major role in reproduction, metabolism and homeostasis. With the help of several transporters present in the Blood Brain Barrier and cerebrospinal fluid insulin reaches the brain. This activates the insulin receptors of brain and thus enhances cognitive abilities. As a result, GLUT 4 is translocated to hippocampal plasma membrane and increase the glucose uptake (19). Scientists found that the response of glucose & hormone stimulation by depolarizing ATP sensitive potassium channels is similar with beta cells and neurons. As the glucose metabolism in brain and pancreas is similar, the brain plays a major role in the production of insulin. Enhanced apoptosis, disturbance in glucose homeostasis and lipid metabolism are considered as the hallmark for developing Type 3 Diabetes Mellitus (19). Insulin and Insulin Growth Factor signaling is essential for the phosphorylation and gene expression of the tau protein. Impaired insulin signaling was found to be a reason for the CNS degeneration in AD. Insulin and Insulin Growth Factor-1 activates intracellular signaling pathways by binding to the receptors at the cell surface. This results in the activation of intrinsic receptor tyrosine kinases which in return phosphorylates IRS molecules. This helps in transmitting signals downstream and inhibit glycogen synthase kinase 3β (GSK-3β). These pathways have critical roles in neurodegeneration (20). There is a role of protein in the progression of Type 2 Diabetes Mellitus to Alzheimer's disease. On the basis of this context, Khyati Mittal etal (19) has proposed 7 hypothesis for this progression.

1) Impairment in the insulin signal transduction, which activates IDE results in diabetes. IDE is responsible for the degradation of insulin and amylin. An elevation of IDE in both type 2 diabetes mellitus and alzheimer's disease results in high degradation of insulin. Thus there will be a downregulation of insulin growth factor- 1 and upregulation of interleukin 1 beta, which results in the oxidative stress of brain. This contributes to the Alzheimer's disease.
2) Insulin resistance interrupts the insulin signaling pathway and retains RAC- beta serine / threonine-protein kinase and contributes to the pathogenesis of Alzheimer's disease (AD).
3) A down regulation of Cathepsin B (CTSB) protein results in the insulin imbalance in body. Interaction of CTSB with APOE results in APP formation which contributes to the pathogenesis of AD.
4) Decreased action of Low-Density Lipoprotein (LRP2) proteins due to an impairment in the insulin signal pathways contributes to the pathology of AD due to the increased expression of APOE.
5) Insulin resistance affects Retinoblastoma Protein (RB) and prevents inhibition of PPARG. This in turn down regulates MAPK pathway and contributes to the pathogenesis of AD.
6) Impaired Insulin Signaling Reduces the insulin affinity for insulin receptor (INSR). An involvement of PIN1 with this regulates the amyloid –β production and contributes the AD pathology.
7) Impaired signaling of IRS1 contributes to the pathology of AD (19).

Experimental studies on rats found that Peroxisome Proliferator – Activated Receptor agonists are effective for AD type neurodegeneration and associated dementia. PPAR works at the nuclear level and activates the gene responsible for insulin signaling mechanisms of the isomers of PPAR, expressed in adult human brain, PPAR-α, PPAR-δand PPAR-γ. PPAR-δ is found abundantly (20).

Conclusion

Due to the greater prevalence of Type 1 and Type 2 Diabetes Mellitus, the newer forms of diabetes are left unrecognized and under treated. Further research on these types of Diabetes Mellitus could pave way for targeted drug therapy. Decreased availability of evidence on this medical condition projects an

increased opportunity for research. Clinical diagnosis of a patient with diabetes should not be just confined to Type 1 and Type 2 Diabetes. Apart from checking the blood glucose level, molecular diagnosis is essential for identifying LADA, MODY and Type 3 Diabetes. Precision in the diagnosis of diabetes plays a big role in defining the appropriate treatment options and its likely responses. Drug of choice also varies among different types of diabetes. Recent research works are oriented towards identifying biomarkers for diagnosis of these newer types, this could reduce the economic burden of genetic testing. Translational biology and Next- generation sequencing (NGS) are some of the promising future prospects in this field of research. Pluripotent stem cell technology can also be considered as a suitable alternative to genomic approaches. However its implementation may not be feasible both clinically and economically. This era of personalized or precision medicine enables to achieve desired therapeutic outcomes following the detection of certain molecular and clinical determinants. Since the diabetes can lead to several other complications, it is necessary to educate the patients regarding the newer forms diabetes and its available treatment. In addition, these emerging types of diabetes turn out to be challenging and difficult to tackle for the healthcare professionals thereby increasing the need for further research in this field.

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