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RESEARCH ARTICLE

MATURITY-ONSET DIABETES OF THE YOUNG (MODY): FIRST CASE REPORTED OF GCK-MODY TYPE IN HATTA HOSPITAL, DAHC, UAE

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Abstract

Maturity-onset diabetes of the young (MODY) is a genetically diverse endocrine disorder of autosomal dominant inheritance characterized by pancreatic β-cell dysfunction.Since the clinical symptoms are so similar, it can be difficult to diagnose MODY accurately, so it is important to consider a patient's family history and any other genetic risk factors when making a diagnosis.Glucokinase (GCK) was the first MODY gene identified; it has been associated with defects in several genes.(1)

Case Presentation:-

A 15 years old female patient referred to endocrine and diabetes department at Hatta hospital with history of prediabetes for about 2 years back.

The patient was presented for evaluation of long-standing elevation in her glycosylated hemoglobin (Hba1c) in the prediabetic range.

This was first noted two years ago on routine blood tests. Mother specifically requested Hba1c as she had gestational diabetes and continued to have Hba1c in the prediabetic range since - off medications. Maternal grandmother has the same. All the patients' siblings have normal level and so do mother's siblings.

She never reported any symptoms but for the past few weeks she woke up multiple times at night to urinate but does not report polydipsia.

The patient reported loss of about 2 kg over the last 5-6 months.

There is no family history of autoimmune diseases.

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She rarely tests her blood glucose levels at home, mother reports all in the normal range.

The patient has regular menses and no symptoms or signs of other endocrinal or developmental disorders, No manifestations of insulin resistance such as acanthosis nigricans.Her vitals within accepted ranges and Blood pressure is 113/78.Height 155 cm (61.02") | weight 53 kg | body mass index 22.06 kg/m².glycosylated hemoglobin (Hba1c) in prediabetic range 5.7% to 6.4%.

Testing was obtained so far shows insulin and C-peptide levels in range, negative anti-glutamic acid decarboxylase antibodies (GAD65), islet cell antibodies and thyroid antibodies. MODY MLPA test is negative as well.also tested remaining autoantibodies, anti-insulin antibodies and zinc transporter cells T8 antibodies (ZnT8 Abs) and were normal.

We discussed that given family history consistent of autosomal dominant pattern, and suspected MODY 2 - GCK mutation.

MODY NGS panel done to complete the evaluation though, and the test came positive for MODY 2 - GCK mutation type, this is the first case reported in Hatta hospital.

Patient was informed about her condition in detail, to continue diet control with lifestyle modification, no treatment required for her condition for the time being and needs regular follow up with the diabetes team including diabetologist, diabetes educator and the nutritionist. Also advised for other family members screening for MODY.

We reported a case of MODY-GCK type in a female patient 15 years old which was diagnosed as prediabetes for about 2 years back.

A diagnosis of type 1 or type 2 diabetes did not seem to be strongly suggested by the age of the patient and the clinical characteristics.

Then MODY screening test done for her, it came positive for GCK gene defect which also known as MODY 2.

The patient started on diet control with lifestyle modification and showed improvement. [8&9]

Discussion:-

Maturity-onset diabetes of the young (MODY) is an autosomal, dominantly inherited form of diabetes that is characterized by an early age of onset (at least one affected family member with an onset before 25 years of age) and pancreatic beta-cell dysfunction. The clinical features of MODY can vary greatly, but typically include an abnormal glucose tolerance test, an absence of ketoacidosis, and the need for minimal or no insulin treatment. These features are suggestive of a genetic defect in the pancreatic beta-cells that results in a reduced ability to produce insulin.[3]

The prevalence of Glucokinase (GCK)-MODY is difficult to assess, this is because the condition is rare and there are usually no visible symptoms, so it is difficult to identify those affected. Furthermore, there is no screening process for GCK-MODY, meaning that the majority of patients remain undiagnosed.[5]

Mody subtypes:

Table 1:- Genes associated with monogenic diabetes[12].

Gene	Protein	Type of diabetes	Characteristic features
HNF1A	HNF-1α	MODY	Progressive β-cell dysfunction, low renal threshold for glucose, low hsCRP, increased HDL and decreased TG, sensitive to SU
HNF4A	HNF-4α	MODY	Progressive β-cell dysfunction, neonatal macrosomia/hypoglycemia, low HDL and normal TG, sensitive to SU
GCK	Glucokinase	MODY	Stable mild hyperglycemia, HbA1c <8% (64

			mmol/mol); no treatment required, complications rare
HNF1B	HNF-1β	MODY	Progressive β-cell dysfunction, associated genitourinary abnormalities, pancreatic exocrine dysfunction/pancreatic atrophy, abnormal LFTs
ABCC8	SUR1	PNDM, TNDM, MODY	Common form of PNDM, less frequent that TNDM; decreased birth weight, treated with high-dose SU
KCNJ11	IRK channel, subunit Kir6.2	PNDM, MODY	Most common PNDM, decreased birth weight, associated developmental delay and epilepsy, treated with high-dose SU
INS	Insulin	PNDM, MODY	10–15% of PNDM, decreased birth weight, requires insulin treatment
ZFP57 (6p22), 6p24 alterations	Zinc finger protein 57	TNDM	Most common form of TNDM, diagnosed in first few weeks of life, resolves by median age of 12 weeks and recurrent later in life in 50–60%, decreased birth weight, associated macroglossia
Mitochondrial genome		MODY	Progressive β-cell dysfunction, 75% sensorineural deafness, other neurological features (MELAS, MERRF); myopathy, cardiomyopathy, renal impairment
KLF11	KLF11	MODY	Rare, pathogenicity not fully established
PAX4	PAX4	MODY	Rare, pathogenicity not fully established
BLK	B-lymphoid tyrosine kinase	MODY	Rare, pathogenicity not fully established
CEL	Carboxyl ester lipase	MODY	Rare, pancreatic exocrine dysfunction/pancreatic atrophy
IPF1	Insulin promoter factor 1	MODY	Rare, pancreatic agenesis in homozygous mutation
NEUROD1	Neurogenic differentiation factor 1	MODY	Rare, associated cerebellar hypoplasia, sensorineural deafness, developmental delay and visual impairment
EIF2AK3	EIF2α kinase 3	PNDM	Rare, AR, associated renal failure, mental retardation, recurrent hepatitis and spondyloepiphyseal dysplasia (Wolcott–Rallison syndrome)
WFS1	Wolframin	PNDM, recent report of MODY	DIDMOAD
RFX6	Regulatory factor X6	PNDM	Rare, associated hypoplastic pancreas and gall bladder, intestinal atresia
PAX6	PAX6	PNDM	Association with brain malformations, microcephaly, microphthalmia, cataract

AR: Autosomal recessive; DIDMOAD: Diabetes insipidus, diabetes mellitus, optic atrophy and deafness; hsCRP: High-sensitivity CRP; LFT: Liver function test; MELAS: Mitochondrial diabetes, encephalopathy, lactic acidosis and stroke-like episodes; MERRF: Myoclonal epilepsy, ragged red fibers in the muscles; MIDD: Maternally inherited diabetes and deafness; MODY: Maturity-onset diabetes of the young; PNDM: Permanent neonatal diabetes mellitus; SU: Sulfonylurea; TG: Triglyceride; TNDM: Transient neonatal diabetes mellitus. Data taken from [12].

The majority of MODY patients are initially misdiagnosed with T1DM or T2DM and because of that are inappropriately. This is because MODY is a rare form of diabetes and is often not considered in the differential diagnosis. It can also be difficult to distinguish MODY from T1DM and T2DM, as the symptoms are similar, so misdiagnosis may occur.[10]

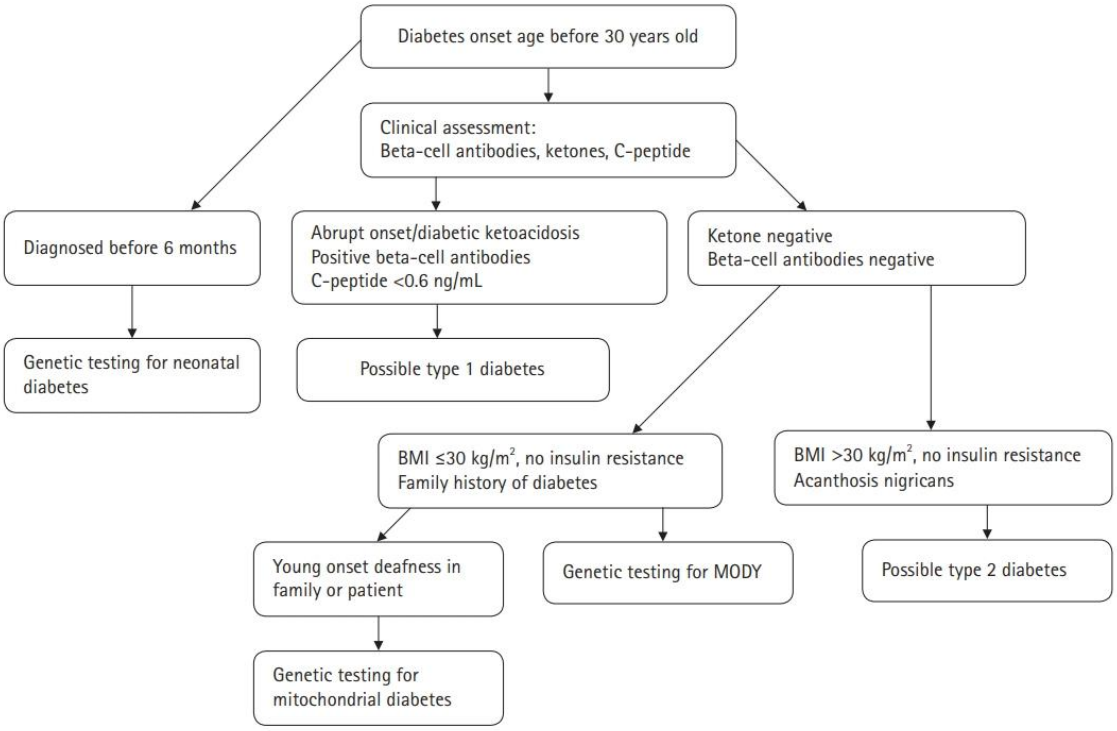

Figure1:- Clinical algorithm to aid the diagnosis ofMODY, BMI, body mass index.[10]

Genetic testing indications:[11]

1. a person who is diagnosed with diabetes before age of 25 without the presence of autoantibodies.
2. Not obese and almost normal body weight
3. positive family history of diabetes
4. regular endogenous insulin production for some years after diagnosis
5. no manifestations of insulin resistance

Genetic testing benefits:[11]

1. To diagnose MODY and differentiate it from type I and II DM
2. To classify MODY subtype for best management: diet (MODY2), sulfonylurea drugs (MODY3, MODY1), or insulin (MODY4, MODY5)
3. To expect the prognosis
4. To identify family members at high risk for diabetes

It is important that healthcare professionals have the right tools and knowledge to accurately diagnose MODY to provide patients with the most appropriate treatment and care.[2]

For example, in cases with MODY-GCK type, anti-diabetic medications are ineffective. This is because the glucose-lowering therapies do not address the root cause of the condition, which is the mutation that causes GCK-MODY. Therefore, even if the therapies were effective at reducing glucose levels, the underlying condition would remain. [2,7], while patients with HNF4A- or HNF1A-MODY responding well to sulfonylureas, due to increased pancreatic insulin secretion. [2,7]

Conclusion:-

The genetic evaluation of a clinical suspicion of MODY is important to confirm the diagnosis and This will enable physicians to choose the way of management more accurately for each patient.

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