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RESEARCH ARTICLE

"IDENTIFICATION OF A NOVEL APPL1 GENE MUTATION IN A SAUDI ARABIAN PATIENT WITH MATURITY-ONSET DIABETES OF THE YOUNG (MODY 14): A CASE REPORT"

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Abstract

Introduction: The need of genetic testing and individualized treatment for diabetic individuals with a family history of the condition is discussed in this case study. It emphasizes the significance of early detection and therapy of maturity-onset diabetes of the young (MODY) and the potential advantages of identifying unique mutations that may contribute to the development of diabetes.

Case Presentation:A Saudi Arabian woman of 50 years old with a strong family history of diabetes was discovered to have a new mutation in the APPL1 gene related with MODY 14. Prior to age 30, the patient had a history of elevated blood sugar, but had never used diabetes medication. Gliclazide and metformin were prescribed to the patient, resulting in a decrease in HbA1c levels.

Conclusion: This case study illustrates the significance of genetic testing in finding novel mutations that may contribute to the development of diabetes and in adapting treatment to the specific needs of individual patients. Detection and treatment of MODY at an early stage helps reduce complications associated with poorly managed diabetes. To completely comprehend the functional repercussions of the APPL1 gene mutation and its impact on the patient's long-term health, additional research is required.

Introduction:-

Diabetes is a chronic metabolic condition defined by hyperglycemia caused by abnormalities in insulin secretion, insulin action, or both [1]. The global prevalence of diabetes is projected to increase to 700 million by 2045, from an estimated 463 million individuals with diabetes in 2019 [2]. In Saudi Arabia, diabetes is also prevalent, affecting an estimated 17.7 percent of the adult population [3].

Maturity-onset diabetes of the young (MODY) is a rare form of diabetes inherited in an autosomal dominant manner and caused by mutations in genes that affect pancreatic beta-cell activity [4]. There are currently 14 subtypes of MODY, each caused by mutations in a different gene [5]. The 23 exons of the APPL1 gene (adaptor protein, phosphotyrosine-interacting with the PH domain and leucine zipper 1) are located in the 3p14.3 region of the

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chromosome. APPL1 is a multifunctional adaptor protein that consists of 710 amino acid residues (aa) and is distinguished by five key functional domains: an NH2-terminal Bin/Amphiphysin/Rvs domain (BAR domain; aa 17–268, identified as a leucine zipper), a central pleckstrin homology domain (PH domain; aa 278–374), a motif between PH and PTB domains (BPP Each domain of APPL1 can bind to lipids with its own specific binding affinity [6].

As an adaptor in the adiponectin signaling pathway, APPL1 also plays an important role in the regulation of insulin metabolism and insulin resistance. Adiponectin, a hormone released by white adipose tissue, has anti-inflammatory and anti-diabetic properties, increases insulin sensitivity, affects sexual and general maturation, pregnancy, and lactation [7,8]. Obesity and metabolic syndrome are linked to a decrease in adiponectin levels. There is a direct interaction between the PTB domain of APPL1 and the intracellular N-terminus of the adiponectin receptors AdipoR1 and AdipoR2. APPL1 mediates fatty acid oxidation and glucose metabolism in adiponectin signaling by activating AMPK (AMP-activated protein kinase) and p38 MAPK (P38 mitogen-activated protein kinases)[8]. APPL1 protein isoforms APPL2 [9] and APPL1sv (which is encoded by a murine splice variant of App1 mRNA [10]) operate as negative regulators of adiponectin signaling, according to reports. In Appl1-deficient animals, adipocyte differentiation is inhibited, and lipolysis is increased in adult adipocytes, whereas APPL1 overexpression has no discernible effect on these processes [11]. APPL1 mediates AMPK phosphorylation in response to adiponectin [12]. Through an interaction with HDAC3 (Histone deacetylase 3), it affects the thermogenesis of brown adipocytes; this phenomenon has promising implications for the treatment of obesity [13].

In this case report, we describe a patient with a strong diabetic family history who was found to have a new mutation in the APPL1 gene, which is related to MODY 14. The detection of this mutation has enabled tailored treatment and control of the patient's diabetes, underscoring the significance of genetic testing for patients with a family history of the disease. The ramifications of this mutation and its potential impact on the patient's long-term health results require additional study.

Case presentation:
We presented a case of a 50-year-old Saudi Arabian woman with a three-generation family history of diabetes. Prior to the age of 30, the patient had a history of hyperglycemia, but no history of diabetic ketoacidosis (DKA). Prior to her recent diagnosis with diabetes mellitus (DM), she had not taken any medications.

Laboratory and genetic testing:
We collected DNA from peripheral venous blood, then sequenced and compared the exons of MODY [1–13]-related genes (HNF4, GCK, HNF1, PDX1, HNF1, NEUROD1, KLF11, CEL, PAX4, INS, BLK, ABCC8, KCNJ11) with reference sequences. All procedures in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee(s) and the Helsinki Declaration (as revised in 2013). The patient provided written informed consent for the publication of this case report and its associated photographs. This journal's editorial office has access to a copy of the written consent for review.The patient was revealed to have a mutation in the APPL1 gene (MODY 14), which is related with the phenotype of young-onset maturity-onset diabetes (MODY). In the gnomADdatabasto particular variant discovered in this patient was c.200>G p. (Glu6gly)chr3:57271566, with heterozygosity and a minor allele frequency (MAF) of 0.07 percent. This variant's classification was of questionable relevance.

Treatment and outcome:
The patient was administered Gliclazide 30 mg and metformin 500 mg TID, resulting in a positive response. Her baseline HbA1c score was 15.8 percent, but after treatment it decreased to 8.1 percent. Due to her genetic susceptibility to diabetes, the patient still requires close monitoring and management of her blood glucose levels.

Discussion and Conclusion:-

The prevalence of diabetes mellitus is increasing all over the world, and this trend can also be observed in Saudi Arabia [14]. This highlights a major public health concern. The estimated prevalence of diabetes in Saudi Arabia in 2013 was 23.9 percent, according to a study that was published in the Journal of Diabetes and its Complications [15]. The study also found that the incidence of diabetes was higher in urban areas and among older age groups [15]. The high prevalence of diabetes in Saudi Arabia can be ascribed to a number of different causes, including urbanization, leading a sedentary lifestyle, and having a genetic predisposition to developing the disease [16].

The discovery of a new mutation in the APPL1 gene in a Saudi Arabian patient diagnosed with MODY 14 underscores the need of conducting genetic testing on patients who have a history of diabetes in their families. Because of its role in the maintenance of glucose homeostasis and sensitivity to insulin, the APPL1 gene has been identified as a possible therapeutic target for diabetes [17]. The exact mutation that was found in this patient, c.200>G p. (Glu6gly)chr3:57271566, has not been described in the scientific literature before and is classified as having unknown significance. However, because it is found in the region of the gene that codes for proteins, it is highly likely to have an effect on the function of the gene.

Maturity-onset diabetes of the young (MODY) is an uncommon form of diabetes that typically manifests itself in people under the age of 25 [18]. It is caused by mutations in genes that govern the function of pancreatic beta-cells and is classified as type 1 diabetes. The detection of particular gene mutations in MODY patients can be of assistance in both the diagnosis and the development of a personalized treatment plan for the disease. The patient in this case report was determined to have a mutation in the APPL1 gene, which is a mutation that has not been documented anywhere else in medical Saudi literature before however, few cases were reported internationally [19,20].

There is evidence that the APPL1 gene has a role in the control of insulin sensitivity as well as glucose homeostasis [21]. The exact mutation that was found in this patient, c.200>G p. (Glu6gly)chr3:57271566, is located in the region of the gene that codes for protein, therefore it is highly likely that this change will have an effect on the gene's function. The patient's response to treatment with gliclazide and metformin demonstrates how important it is for patients diagnosed with MODY to receive medication that is individualized to their specific needs. Despite the fact that diabetes cannot be cured, early detection and individualized treatment can assist to prevent or delay the onset of complications and improve long-term outcomes [22]. The patient's reaction to treatment with gliclazide and metformin is further evidence that tailored treatment may offer patients with MODY potential benefits.

In conclusion, the finding of a unique APPL1 gene mutation in this Saudi Arabian patient with MODY 14 emphasizes the significance of genetic testing and individualized treatment for diabetic patients who come from families with a history of the disease. It is necessary to do additional study in order to acquire a comprehensive understanding of the functional ramifications of this mutation as well as the potential influence it may have on the patient's long-term health outcomes. With continued advances in genetic testing and precision medicine, it is hoped that more effective and personalized treatments can be developed for patients with diabetes and other complex genetic disorders.

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