VOLUME - 12, ISSUE - 09, SEPTEMBER - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Diabetology

RARE CASE OF PERMANENT NEONATAL DIABETES MELLITUS (MONOGENIC DIABETES) WITH LATE CHILDHOOD PRESENTATION NOT REQUIRING INSULIN THERAPY

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ABSTRACT A 7-year-old boy presented with very high blood glucose (486mg %) with history of significant weight loss. With presumptive diagnosis of type-1 diabetes, insulin therapy was advised along with antibody tests (GAD and IA-2) for type-1 diabetes. Parents refused for Insulin therapy; glimepiride started. Within a week, blood glucose level improved remarkably, and antibodies commonly evaluated for type-1 diabetes was negative. Genetic testing for Maturity onset diabetes of the young (MODY) was done and found positive for KCNJ11 gene which usually presents with neonatal diabetes requiring Insulin therapy, but this case was a late onset variation not requiring insulin.

KEYWORDS :

Case

A 7yr old boy came to us in February 2020 with incidental detection of high blood glucose. Parents noticed a significant weight loss in their child so they did his random blood glucose at home which came out to be 454mg%. The repeat blood glucose at our clinic was 486mg%. The boy was not having any osmotic symptoms or symptoms of ketoacidosis. His urinary ketone with dipstick method was negative.

Family History

His father is under our follow up for last 10yrs, registered as a case of Type 2 diabetes mellitus (T2DM) and well-controlled on oral antidiabetic drugs. He was diagnosed as a case of T2DM at the age of 32yrs. His grandfather is also a known case of T2DM, details of whom are not available. His mother is not a known case of T2DM and there is no history of consanguineous marriage. The two older siblings of the boy do not have a history of diabetes.

Clinical Examination

The blood pressure at the time of presentation was 102/66 mmHg and pulse rate 110/min. The weight was 25kg and with height of 112cms, the BMI calculated was 19.9, placing the BMI for age at the 97th percentile for 7-year-old boys.

Investigations

The HbA1C of the patient with HPLC method (expressed in NGSP units) was 12.9%, The Glutamic acid decarboxylase antibodies (GAD antibodies) and IA2 antibodies were negative. The other blood investigations related to liver, kidney and thyroid were normal. The Ultrasound abdomen of the patient was also normal.

Clinical Course

As soon as the child presented to us, we planned to start insulin but parents were very reluctant. On examination it was observed that the patient was slightly obese and may be having a remote possibility of not having T1DM. On getting reassurance from the parents about regular visits, Glimepiride 2mg bd was started and they were called for review after two days with the reports of random blood glucose and antibodies specified above.

In the next visit the blood glucose level by glucometer was 352mg% and antibodies were negative. According to these reports T1DM was almost ruled out and now T2DM or Monogenic Diabetes Mellitus were to be considered. Since T2DM is rarely seen before 12yrs of age, and with a family history of diabetes in previous two generations, there was a strong possibility of Monogenic Diabetes.

Parents kept monitoring his blood glucose at home and his fasting blood glucose levels gradually came down to around 110mg% and prandial levels varied depending upon his diet. His HbA1C after 2 months was 8.1%. We all motivated the child to be more active and to play more outdoor games along with usual dietary restrictions as for a person living with type 2 diabetes mellitus. Gradually his Glimepiride dose was tapered down from2mg bd to 2mg od.

Genetic Testing

The blood sample was sent to MEDGENOME LABS LTD at Bangalore for the study of genomics of diabetes and the report was received in three weeks. Next-generation sequencing revealed the presence of mutation p. Arg221Cys at exon 1 of gene KCNJ11, a variant of uncertain significance (VUS). A heterozygous missense variation in exon 1 of the KCNJ11 gene (chr11: g.17387431G>A; Depth: 401x) that results in the amino acid substitution of Cysteine for Arginine at codon 221 (p. Arg221Cys; ENST00000339994.5) was detected.

DISCUSSION

What are monogenic forms of diabetes?

The most common forms of diabetes type 1 and type 2 are polygenic, meaning they are related to a change or defect in multiple genes. Environmental factors such as obesity and insulin resistance in the case of T2DM and a combination of genetic, environmental, and immunologic factors in case of T1DM also play a key role in development of polygenic forms of diabetes.

Some rare forms of diabetes result from mutations in a single gene and are called monogenic diabetes. It may be dominantly or recessively inherited or maybe a de novo mutation and hence a spontaneous case. In children almost all monogenic diabetes results from mutations in the genes that regulate beta cell function. Rarely monogenic diabetes occurs from mutations resulting in severe insulin resistance. Monogenic forms of diabetes account for about 2 to 5% of all cases of diabetes (1-5).

Why diagnose monogenic diabetes?

Most patients with genetically proven monogenic diabetes are initially incorrectly diagnosed as either type 1 or type 2 diabetes mellitus.

When the suspected diagnosis of T1DM in children may be wrong?

1) a diagnosis of diabetes before 6 months of age. (6)
2) family history of diabetes with a parent affected at younger age (7)
3) evidence of endogenous insulin production even after 3 years of diagnosis of diabetes with detectable serum C peptide
4) when pancreatic islet autoantibodies and GAD autoantibodies are absent specially if measured at diagnosis, (7-10).

When the suspected diagnosis of T2DM in children may be wrong?

1) not markedly obese or family members living with diabetes who are also of normal weight
2) acanthosis nigricans not detected
3) no evidence of insulin resistance with fasting C peptide within normal range (11-14)

Making a diagnosis of monogenic diabetes

While in T1DM and T2DM there is no single diagnostic test, this is not the case in monogenic diabetes, where in 80% of cases a molecular genetic diagnosis can be made by DNA testing.

Given the limited resources available it is vital that these tests are used in situations where they are likely to be positive which may change the plan of management. This will involve careful clinical selection and performing tests like C peptide and auto antibody measurement before molecular genetic tests.

Specific subtypes of monogenic diabetes

1 neonatal diabetes mellitus (NDM)
2 maturity onset diabetes of young (MODY)
3 Syndromic forms of monogenic diabetes

Neonatal diabetes mellitus (NDM)

Neonatal diabetes is diagnosed within 6 months of life and mostly is insulin requiring diabetes but may be controlled on sulfonylureas. Clinically two subgroups have been recognised: transient neonatal diabetes mellitus (TNDM) and permanent neonatal diabetes mellitus (PNDM).

TNDM gets resolved at a median of 12 weeks of age and then does not require any treatment although as many as 50% of cases would ultimately relapse (15, 16). In contrast PNDM requires continued insulin use from diagnosis onwards (17,18). Most of these patients will be found to carry a mutation in one or two genes encoding for the ATP-sensitive potassium channel (K-ATP channel) of the pancreatic beta cells (15-18). These genes are termed KCNJ11 and ABCC8, encoding the KIR 6.2 and SUR subunits of K-ATP channel respectively.

Presence of mutations in these two genes leads to defective K-ATP channel which is unable to close in response to increasing intracellular ATP levels, thereby disrupting endogenous insulin release. However, patients with certain specific mutations are still able to close their K-ATP channel in response to sulfonylureas (21).

Our patient in the above case had mutation of uncertain significance or Variant of Uncertain Significance (VUS) in the gene KCNJ11. It means at the time of interpretation, there was not sufficient evidence to determine if the variant is related to the disease or not (22). Genetic study of other affected members of the family are needed to confirm it. However, KCNJ11 gene mutations have been previously associated with NDM.

While KCJN11 mutations most commonly cause neonatal diabetes mellitus (NDM), there are case reports of these mutations presenting with childhood and later-onset diabetes mellitus. Yorifuji et al describe a 4-generation family with different presentations of diabetes including TNDM, childhood onset and adult-onset diabetes associated with novel mutation p.C42R in KCNJ11. (19). D'Amato et al described a proband with TNDM in a family with presentations at different ages ranging from neonatal, at 14yrs and 26yrs (20).

CONCLUSION

It is important to correctly diagnose monogenic diabetes as it can predict the clinical course of the patient, explain other associated clinical features, and most importantly, guide the most appropriate treatment. In addition, making a diagnosis will have implications for other family members often correcting the diagnosis and treatment and appropriate genetic counselling. Genomic sequencing should be done in all patients of diabetes who phenotypically do not fit into T1DM or T2DM, as it may be helpful to make an accurate diagnosis and provide the best treatment options.

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