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Case Report

A Case Report of Maturity Onset Diabetes in Young with Glomerular Cystic Kidney Disease

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Abstract

The most common known forms of diabetes are type 1, an autoimmune disorder with auto antibodies and type II which is multi-factorial influenced by genetics, environment. Another form of diabetes is MODY (maturity onset diabetes in young), the most common form of monogenic diabetes, seen in non-obese children, adolescents and young adults. MODY a rare condition, accounts for 1–5% of all cases of DM and 1–6% of paediatric diabetes. This is non-ketotic and patients have no antibodies. Hepatocyte Nuclear Factor-1Beta is one of the several genes associated with this disease, causing beta cell dysfunction and extrapancreatic manifestations involving kidney, liver and intestines. In the present case glomerular cystic kidney disease is identified in a young male with diabetes raising clinical strong suspicion of maturity onset diabetes, which later showed Hepatocyte Nuclear Factor-1Beta mutation. A 17-year-old male, presumed type-1 diabetic who was under regular follow up with an endocrinologist, presented with elevated serum creatinine and protein in urine. On referral to our nephrologist, further evaluation was done when cortical kidney cysts were observed on imaging and on biopsy glomerular cystic kidney disease was identified. Genetic analysis revealed heterozygous missense variant of Hepatocyte Nuclear Factor-1Beta on Exon 4, thereby a final diagnosis of maturity onset diabetes in young-hepatocyte nuclear factor-1beta considered. His condition was stable during follow-up, despite the fact that chronic kidney disease is a progressive illness. Interdisciplinary approach helps in accurate typing of diabetes which has a bearing on prognosis and treatment.

Keywords: Maturity Onset Diabetes of the Young, Chronic Kidney Disease, Glomerular Cystic Kidney Disease, Renal Cysts and Diabetes Syndrome, Hepatocyte Nuclear Factor-1Beta, Genetic Testing.

INTRODUCTION

In 1974, Tattersall and Fajans coined the term maturity onset diabetes of the young (MODY) [1]. The *HNF1B* mutation accounts for less than 5% of MODY. This mutation may impact the regulation of genes within the liver, kidneys, intestines, lungs or ovaries. Patients can present with abnormalities such as renal cysts, dysplasia, renal tract malformations, or hypoplastic glomerulocystic kidney disease [2]. Bernstein defined Glomerular cystic kidney disease as widening of Bowmans space, 2-3 times the normal, with at least > 5% cysts containing atrophic glomeruli. He classified GCKD as (a) inheritable syndromic as in this case, (b) inheritable non syndromic, (c)as glomerular cysts in dysplastic kidneys. Hence when glomerular cystic kidney disease is identified, one has to look for syndromic association or acquired causes like obstruction [3].

This case study, describes a 17-year-old boy with presumed type 1 diabetes, with GCKD identified on biopsy suggesting a syndromic association, prompting genetic analysis which revealed mutation in the hepatocyte nuclear factor-1 beta (HNF1β) gene, thereby considering the final diagnosis of MODY-HNF1beta.

CASE PRESENTATION

A 17-years-old boy presumed to be Type 1 diabetic was referred to the nephrologist with high level of serum creatinine and protein in urine. On physical

examination the patient was conscious, with body temperature 98.6 °F, 99% SPO2 on room air, blood pressure 110/71 mm Hg, heart rate 88 beats/ minute and normal respiratory rate.

Results of laboratory investigations were as follows; Fasting glucose:154 mg/dl, HbA1C: 10.30 %, elevated serum creatinine: 2.00 mg/dl. Complete urine analysis reveals acidic pH 5.5, traces of protein and glucose, protein-spot urine: 47.987 mg/dl, creatinine-spot urine: 72.10 mg/dl in urine, calcium: 9.50 mg/dl, serum uric acid: 8.5mg/dl. Due to the increased levels in serum creatinine, physician suggested visual acuity (VA) test, optical coherence tomography (OCT) for the diagnosis of diabetic retinopathy (DR) and it was found to be normal. DMSA (dimercapto succinic acid) scan was done and did not reveal any scar on the kidneys. Real time ultra sonography of abdomen and pelvis showed normal sized kidneys with two simple cortical cysts in the upper pole of right kidney, largest measuring 12mm x 10 mm in size (Figure 2). Laboratory results revealed elevated levels of Parathyroid hormone (173.60 pg/ml) suspecting chronic kidney disease due to RCAD syndrome.

As he has no diabetic retinopathy and no scar on the kidneys, the patient was suggested kidney biopsy to evaluate the cause of kidney dysfunction with the clinical suspicion of non-diabetic kidney disease.

Kidney biopsy revealed all viable glomeruli, with mildly dilated (Figure 1A) to markedly enlarged bowman's space with shrunken tuft (Figure 1B) and (Figure 1C) involving at least 50% of the glomeruli. There is no significant membrane thickening, mesangial widening, increase in cellularity or segmental sclerosis. Few other empty cystic spaces noted, possibly of glomerular origin (Figure 1D). There was also evidence of patchy mild tubular injury with mild tubular dilation, with loss of nuclei and outpouchings in one of the tubules (Figure 1E). Focal tubules with macula densa like nuclear crowding (Figure 1F).

Considering a syndromic disorder genetic testing was done which revealed heterozygous missense variant of Hepatocyte Nuclear Factor-1Beta (HNF1β) (NM.000458.4: c.1006dup, p. His336ProfsTer24 on Exon 4 along with sequence variation in PKHD1 genes. The patient was then relabelled as Maturity onset diabetes of the young (MODY) from type I Diabetes. A proper genetic counselling was given to the patient and his family. He was managed with angiotensin receptor blocker Inj. Insulin and Phosphate binders. Up on the next follow up there was no improvement in the patient's condition, and no progression in the kidney disease as well, with stable condition of the patient.

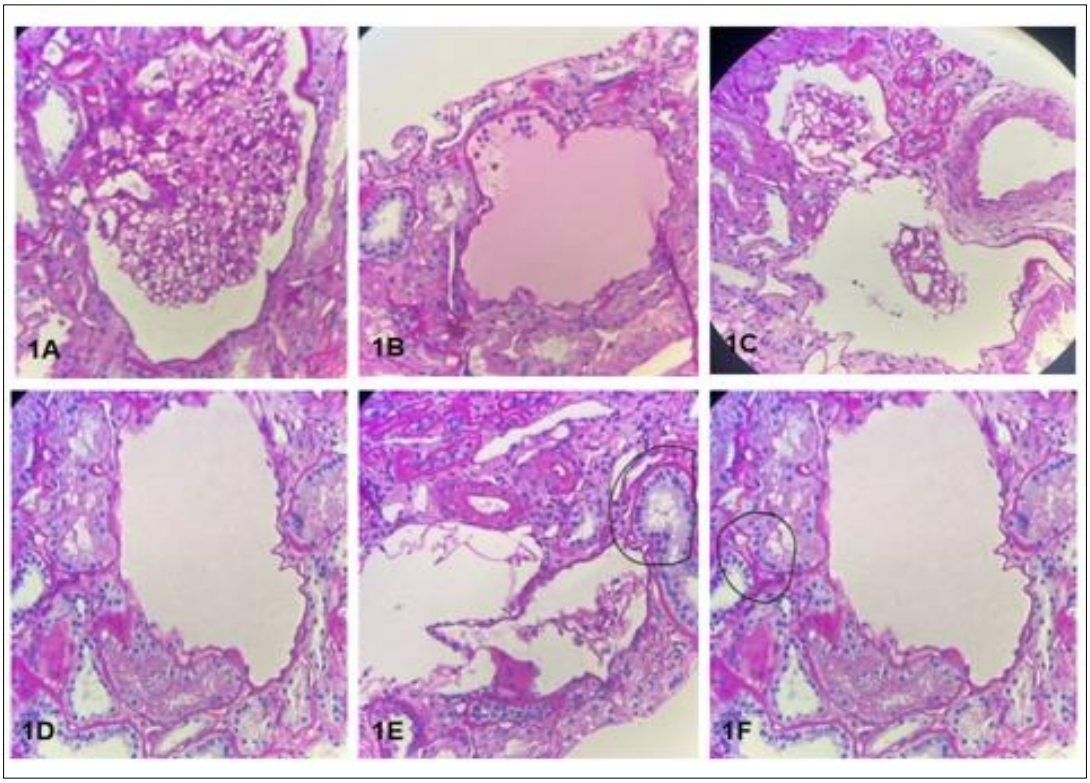

Figure 1: (A) Mildly dilated Bowman's space, (B) Enlarged Bowmans space, (C) Enlarged Bowmans space with shrunken tuft, (D) Empty cystic spaces, (E) Patchy tubular dilation, (F)Macula densa like nuclear crowding.

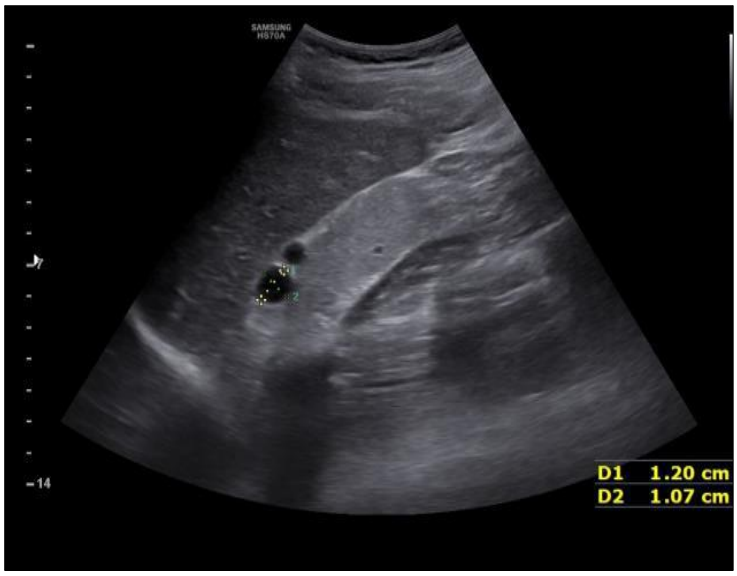

Figure 2: Ultrasound of right kidney showing two simple cortical cysts

DISCUSSION

Hepatocyte nuclear factor 1 beta (HNF1B) plays an important role in embryonic development of kidney, pancreas, liver, genital tract, and gut. Heterozygous germ line mutations of HNF1B are associated with the renal cysts and diabetes syndrome (RCAD) [4].

Renal cystic disease constitutes the predominant characteristic of the HNF-1β phenotype. In 83% of the cases, renal cysts have been identified through ultrasound imaging. Yet biopsy is the most accurate method for diagnosing, staging, and predicting parenchymal kidney disease. Renal biopsy not only yields a histological clue for the primary diagnosis but also makes it possible to assess the prognosis of underlying renal disease and thus enables to provide appropriate therapy [5].

Ultrasonography is a useful tool for identifying cysts with exact location, evaluating cyst complications like tumors, abscesses and infections within or surrounding the kidneys [6]. In our patient with the help of ultra sonography, two simple cysts were detected in the right kidney. Biopsy identified them as Glomerular cysts, which made us to go for genetic analysis. A multigene NGS analysis is helpful in accurately identifying the underlying genetic disease as similar phenotype could be expressed by various genotypic disorders.

CONCLUSION

Hepatocyte Nuclear Factor-1Beta (HNF1β) gene mutation is an uncommon causes of early onset diabetes/ MODY, Genetic testing is necessary to reveal the mutations for accurate typing of diabetes, prognostication and as a guide for further family counselling. Early detection with the possibility of gene therapy could be the future prospect.

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Ethical Approval: Not required

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