An interesting unfolding of the diagnosis of hepatocyte nuclear factor-1 beta (HNF1β) monogenic diabetes

**Abstract**

The HNF1B gene plays an important role in endodermal development, and mutations of HNF1B are associated with the renal cysts and diabetes (RCAD) syndrome. Other than renal cystic malformations and monogenic diabetes, various other abnormalities have been described depending on HNF1β expression. Molecular diagnosis has huge implications for the treatment of the patient and their family members.

We present a case of RCAD syndrome with a previously unreported mutation. A 49-year-old man with diabetes mellitus was admitted with worsening chronic kidney disease requiring haemodialysis. He developed recurrent, unexplained hypoglycaemia despite discontinuing insulin, making the diagnosis of type 1 diabetes mellitus questionable. He had detectable serum C-peptide (742 pmol/L), and anti-GAD and anti-pancreatic islet cell antibodies were negative. Abdominal imaging revealed renal cortical cysts and atrophic pancreas. A significant family history of diabetes mellitus with renal disease was also established which prompted us to suspect mutation of the HNF1B gene.

Genetic testing confirmed the diagnosis: he was found to have a novel HNF1B missense mutation p.R165C previously not reported. This case study identified a mutation previously unreported thereby expanding the spectrum of HNF1B gene mutations. Copyright © 2017 John Wiley & Sons.

**Key words**

HNF1β; renal cysts and diabetes; monogenic diabetes

**Introduction**

Monogenic diabetes results from mutations that reduce β-cell function and accounts for 1–2% of diabetes cases. It develops before the age of 25, runs in families and has an autosomal dominant inheritance. There are many types with different genetic abnormalities, treated by diet or oral hypoglycaemic agents, and insulin therapy is not usually needed. Definition of the genetic subgroup is essential for appropriate treatment, genetic counselling and prognostic information.

Renal cysts and diabetes (RCAD) is one subtype accounting for 1% of the total cases of monogenic diabetes in the UK. It can cause diabetes, renal developmental disorders, abnormal liver function, hypomagnesaemia, and hyperuricaemia. It is caused by mutation in the HNF1B gene located on chromosome 17q with 9 coding enzymes. HNF1B is a member of the homeodomain-containing superfamily of genes. It encodes the transcription factor involved in endodermal development which explains the multi-organ involvement in affected patients. The first HNF1B mutation, R177X, was described in a Japanese family with maturity-onset diabetes of the young (MODY) in 1997. Several types of mutations have been reported subsequently, and the intron 2 splice site appears to be a mutational hotspot. Haploinsufficiency has been described as the underlying mechanism. Spontaneous mutations are common (32–58%) and no clear correlation between type/position of mutations and clinical phenotype has been established. Wide variability within a given family with the same mutation has been reported.

We report a novel HNF1B missense mutation p.R165C previously not reported. This case study identified a mutation previously unreported thereby expanding the spectrum of HNF1B gene mutations.

**Case report**

A 49-year-old slim, Caucasian man was referred to us as type 1 diabetes mellitus with deteriorating chronic kidney disease while recovering from a
below-knee amputation. His glycaemic control was historically poor, but the latest HbA1c was only 37mmol/mol.

He experienced recurrent hypoglycaemia despite being on very small amounts of insulin. He was diagnosed as having type 1 diabetes at the age of 21 years and was on insulin therapy. His mother, father and three brothers were reported to have type 1 diabetes. Two of his three brothers with type 1 diabetes also had some renal problems, however; the details of their renal problems were not available. He was a smoker and consumed alcohol in moderation.

For a few years prior to this admission to hospital, his insulin requirement had been decreasing consistently. This was alongside progressive deterioration in renal function. He was eventually treated with basal insulin only. His current admission to hospital was due to deteriorating renal function and an infected diabetic ulcer on his left foot, needing surgical intervention. He had macrovascular complications associated with diabetes – such as ischaemic heart disease, peripheral vascular disease, cerebral vascular disease, dyslipidaemia, hypertension, and erectile dysfunction. He also had micrvascular complications such as end-stage renal disease, pre-proliferative retinopathy, painful mixed peripheral neuropathy and autonomic neuropathy.

While in hospital, his insulin doses were continually reduced to manage the recurrent hypoglycaemia, and were eventually stopped. Despite stopping insulin, he did not develop hyperglycaemia and diabetic ketoacidosis, raising doubts about the diagnosis of type 1 diabetes.

Investigations (Table 1) revealed an HbA1c of 37mmol/mol. Thyroid functions and 9am cortisol were unremarkable, ruling out associated thyroid dysfunction and primary cortisol deficiency as causes of hypoglycaemia. His C-peptide was 742 pmol/L, indicating endogenous insulin production and thus ruling out type 1 diabetes. Furthermore, serum anti-pancreatic cell and anti-glutamic acid decarboxylase (GAD) antibodies were negative. He had abnormal liver function with elevated serum levels of liver enzymes. His magnesium was normal and urate levels were not done.

Ultrasonography and subsequent computerised tomography (CT) scan of the abdomen revealed the presence of bilateral renal cysts (1.1 x 1.0 x 0.9cm at the upper pole of the right kidney and 0.6 x 0.6 x 0.7cm at the mid pole of the left kidney) and medullary calcification, but were otherwise normal. There was normal liver and atrophic pancreas on imaging.

These findings along with evidence of endogenous insulin secretion with negative antibodies, with a strong family history of young-onset diabetes and renal disease prompted the diagnosis of HNF1B monogenic diabetes. His genetic test confirmed that he had a heterogeneous missense mutation of the HNF1B gene in the exon 2 location (DNA prescription c.493C>T; protein description p.Arg165Cys [p.R165C]). This mutation has not been reported previously but two different missense mutations at this position – p.R165H8 and p.R165P9 – have been reported in families with RCAD.

Discussio

Renal cortical cysts, decreasing insulin requirement on the background of type 1 diabetes, and a strong family history of young-onset of diabetes mellitus and associated renal problems prompted us to think of a possible HNF1B mutation.

A meta-analysis done by Alvelos et al. indicates that at least 106 different HNF1B mutations in 236 mutation-positive families have been reported so far. The reported number of mutations can be categorised into: (i) gross deletions (34%); (ii) missense mutations (31%); (iii) frame-shift deletions or insertions (15%); (iv) nonsense mutations (11%); and (v) splice-site mutations (8%). Our case report is a further addition to the current list of reported missense HNF1B mutation causing RCAD.

Renal manifestations in those with HNF1B mutations can vary from normal kidney function to end-stage renal disease. The time of onset of renal disease in patients with RCAD syndrome is variable: it can start anywhere from intrauterine life to middle age, with the mean age of 21 years. One of the

<table>
<thead>
<tr>
<th>Relevant investigations</th>
<th>Value</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>Glycated haemoglobin (HbA1c)</td>
<td>37mmol/mol</td>
<td>–</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (eGFR)</td>
<td>22ml/min/1.73m²</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Adjusted calcium</td>
<td>2.58mmol/L</td>
<td>2.20–2.60</td>
</tr>
<tr>
<td>Inorganic phosphate</td>
<td>1.04mmol/L</td>
<td>0.80–1.50</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.73mmol/L</td>
<td>0.70–1.00</td>
</tr>
<tr>
<td>Bilirubin total</td>
<td>13umol/L</td>
<td>&lt;21</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>50 U/L</td>
<td>&lt;35</td>
</tr>
<tr>
<td>Gamma-glutamyl transpeptidase</td>
<td>85 U/L</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>332 U/L</td>
<td>30–130</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>1.8mU/L</td>
<td>0.30–6.00</td>
</tr>
<tr>
<td>Free T4</td>
<td>15.2pmol/L</td>
<td>10.0–22.0</td>
</tr>
<tr>
<td>9am cortisol</td>
<td>611nmol/L</td>
<td>140–500</td>
</tr>
<tr>
<td>C-peptide</td>
<td>742pmol/L</td>
<td>190–990</td>
</tr>
<tr>
<td>Anti-pancreatic cell antibody</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td>Anti-glutamic acid decarboxylase (GAD) antibody</td>
<td>Negative</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 1. Laboratory parameters on admission
phenotype surveys on all reported subjects with HNF1B mutation showed that at least 66% of the patients had renal impairment with varying histology;2 2% of the patients had horseshoe kidneys or a single kidney.3 There appears to be no correlation between genotype and phenotype.8 The most specific phenotype for HNF1B mutation is familial hypoplastic glomerulocystic kidney disease.9 Eighty-six percent of patients with HNF1B mutation have renal impairment and 15% of them have been reported to require dialysis or renal transplantation.8 The renal dysfunction found in these patients is thought to be due to renal developmental abnormalities rather than diabetic nephropathy.3 The management of renal disease is usually supportive based on individual cases.

In our patient, it is difficult to ascertain the cause of renal failure. He had cystic renal disease confirmed on radiological studies, suggesting that his renal impairment could have been due to the RCAD syndrome. However, he also had other associated micro- and macrovascular complications of diabetes mellitus, making associated diabetic nephropathy highly probable. Renal biopsy would have greatly helped us establish the exact cause of his renal disease; however, his clinical condition precluded this procedure.

The prevalence of diabetes mellitus in HNF1B mutation carriers is 45%. Again, the time of onset is variable: from two weeks after birth to 63 years of age, with the mean age of onset being 26 years.2 There is wide phenotype variability reported, from normal glucose tolerance to insulin-treated diabetes presenting with ketoacidosis. The main pathophysiology is reduced insulin secretion due to β-cell dysfunction and pancreatic atrophy, invariably requiring insulin therapy.3 Endogenous insulin production is present and patients with diabetes are not necessarily insulin dependent.10

Our patient developed diabetes in his early 20s and required insulin therapy. He had evidence of pancreatic atrophy on abdominal CT scanning. There was no clinical evidence for exocrine pancreatic dysfunction and there was endogenous insulin production. In patients with HNF1B mutation, diabetes complications are highly prevalent.11 Our patient had both micro- and macrovascular complications associated with diabetes.

HNF1B mutation is also associated with abnormalities other than diabetes mellitus and renal disease. These depend on HNF1B gene expression in different organs. Genital tract and reproductive system abnormalities such as Mullerian duct abnormalities (vaginal aplasia, rudimentary uterus, bicornuate uterus, uterus didelphys and double vagina) in females, and bilateral agenesis of vas deferens, large epithidymal cysts and asthenospermia in males, have been reported.3 Our patient did not have any evidence of genital abnormalities. Abnormal liver function tests with raised alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (γGT) without jaundice or liver insufficiency are well known to be associated with HNF1B mutation.12 Liver appearances are usually normal on ultrasonography. This was the case in our patient.

Hypomagnesaemia, hyperuricaemia, young-onset gout and psychiatric disorders have also been reported;3 however, our patient did not have any evidence for these. Screening for HNF1B gene abnormalities in family members of the affected patient is paramount since early recognition will allow annual surveillance for the development of diabetes and renal disease. This will enable timely intervention and help prevent complications of both. First-degree relatives of the affected need to be referred for local MODY genetic counselling and further screening is guided by the probability of having RCAD as outlined in the guidelines provided by the Exeter team at the Diabetes Research Department and the Centre for Molecular Genetics.13 Our patient’s details have been passed on to the local MODY genetic counselling team for the screening of family members.

Conclusion
Our patient had severe cystic kidney disease and diabetes mellitus with a novel missense mutation of the HNF1B gene. Our case report identifies a previously unreported mutation of the HNF1B gene, thereby expanding the spectrum of known mutations associated with RCAD. It is important to have a high index of suspicion for HNF1B mutation in a young non-obese patient with diabetes and slowly progressive nephropathy, especially with renal cysts and pancreatic atrophy. Early diagnosis and timely management are important in preventing avoidable complications. Our case reiterates the importance of genetic testing since this has huge implications regarding definitive diagnosis, prognosis, treatment and screening of family members.

Acknowledgements
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Declaration of interests
There are no conflicts of interest declared.

References
References are available in Practical Diabetes online at www.practicaldiabetes.com.
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