Von Hippel–Lindau disease: an important differential diagnosis of polycystic kidney disease

G. Browne¹, J. A. Jefferson², G. D. Wright², A. E. Hughes³, C. C. Doherty², N. C. Nevin³ and J. A. B. Keogh¹

¹Renal Unit, Meath Hospital, Dublin, Ireland; ²Mary McGeown Regional Nephrology Unit, Belfast City Hospital, Belfast; ³Department of Medical Genetics, Queen’s University of Belfast, Belfast, N. Ireland

Abstract Von Hippel Lindau disease is a dominantly inherited familial cancer syndrome, characterized by retinal, spinal, and cerebellar haemangioblastomas, renal cell carcinomas, and phaeochromocytomas. Cysts of the kidney and pancreas may also occur.

We describe a large three-generation Irish family with VHL disease who initially presented with features typical of autosomal dominant polycystic kidney disease. Eight clinically affected individuals were found. Visceral complications were particularly prominent within the family. There were no cases of retinal angiomata or phaeochromocytoma. The diagnosis was confirmed by genetic linkage analysis in this family, although the exact mutation has yet to be defined.

Key words: autosomal dominant polycystic kidney disease; von Hippel–Lindau disease; genetic linkage analysis; visceral complications; genetic characteristics

Introduction

Von Hippel–Lindau (VHL) disease is an autosomal dominant familial cancer syndrome occurring once in every 36 000 live births [1]. Disease expression is variable. The most common complications include retinal angiomatosis (59%), cerebellar haemangioblastomas (59%), spinal haemangioblastomas (13%), and renal cell carcinomas (28%) [2]. Renal cell carcinomas (RCC) may be multifocal and bilateral and occur at a younger age than the sporadic form. Other complications include renal, pancreatic, and epididymal cysts and, less commonly, phaeochromocytoma [2].

The VHL gene has recently been identified on chromosome 3, p25–26 [3]. The gene functions as a recessive tumour suppressor gene following Knudson’s two-hit theory of carcinogenesis [4,5]. In familial cancers one mutation in the tumour suppressor gene is inherited and a second somatic mutational event occurs in the wild-type allele leading to malignancy. This second hit has been demonstrated in tumour samples by loss of heterozygosity studies [6]. A wide range of both germline and somatic mutations have now been described, including large deletions, missense and nonsense mutations, splice mutations and in-frame insertions [7–9].

The aim of this observational study was to describe the clinical and genetic characteristics of a large Irish kindred presenting with renal cystic disease and renal impairment (Figure 1).

Subjects and methods

The proband (II3) was a 43-year-old woman with a history of hypertension and frequent urinary tract infections who presented with advanced chronic renal failure (serum creatinine 579 μmol/l). A diagnosis of polycystic kidney disease had been made on renal ultrasound, which showed bilaterally enlarged kidneys with multiple cysts and unusually intracystic calcification. Her renal function deteriorated and she required haemodialysis. In July 1992, she complained of macroscopic haematuria. CT scan of abdomen at that time demonstrated a solid calcified mass in the upper pole of the left kidney and multiple pancreatic cysts. She underwent a radical left nephrectomy and histology confirmed renal cell carcinoma. Multiple renal cysts were noted throughout the kidney consistent with ADPKD. There was no evidence of microscopic tumour foci within the remaining kidney tissue. Postoperatively she developed pulmonary consolidation and she died 2 months later of pulmonary metastases. Three siblings (II2, II4, II5) had undergone renal ultrasonic examination in another centre. A diagnosis of ADPKD was made in each case.

In 1992 a second sibling (II4) age 40 years developed macroscopic haematuria. CT scan of abdomen showed a large right renal mass and multiple renal and pancreatic cysts (Figure 3). A right nephrectomy was performed confirming renal cell carcinoma. In 1994 a spinal haemangioblastoma was diagnosed by MRI and resected, with minimal neurological deficit. The finding of a second family member with renal cell carcinoma suggested the alternative diagnosis of von Hippel–Lindau disease and a family screening programme was instituted.
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Figure 1. Family pedigree. □ males, ○ females. Filled symbols are affected individuals. Numbers below family members represent allele scores for the marker D3S1038 flanking the VHL gene.

Figure 2. CT scan of abdomen. Renal and pancreatic cysts. Large left renal mass with calcification.

Thirty-three family members underwent clinical screening including full physical examination, urinalysis, blood for biochemical analysis and tumour markers. Ophthalmology examination was performed on all patients. All patients underwent abdominal ultrasound and if necessary CT scan of abdomen and brain. Urinary and plasma catecholamines were measured and blood was taken for DNA extraction.

Six further patients, not including the proband (II3) and her female sibling (II4), were diagnosed on clinical findings. Two patients were deceased: the proband (II3) and her male sibling (II7), who died of metastatic renal carcinoma in 1979.

Three patients (III6, II5, II2) aged 13, 39 and 48 years, had radiological evidence of renal and pancreatic cysts without solid lesions. They continue to have normal renal function to date. Two patients (III7, III21), aged 20 and 22 years, had cerebellar haemangioblastomas which were operable. Both patients had radiological evidence of bilateral renal cysts.

One 19-year-old pregnant female (III5) had asymptomatic bilateral renal cysts and bilateral renal tumours. Following
successful delivery, she underwent laparotomy and both tumours were excised, sparing the remaining kidney tissue. The tumours were encapsulated and found to be low grade, stage 1 clear cell carcinomas. During subsequent follow-up, a 15-year-old female (III 11) has developed a cerebellar haemangioblastoma.

**Linkage analysis**

DNA was extracted from the venous blood of 38 family members and analysed for the inheritance of informative polymorphic microsatellites at the PKD1 (D16S283 and D16S291) and VHL (D3S1038) gene loci. The polymerase chain reaction (PCR) was used to amplify the polymorphic regions of DNA under standard conditions. The products were resolved by polyacrylamide/urea denaturing gel electrophoresis and visualized by autoradiography or silver staining.

The family had initially been diagnosed as having ADPKD, and linkage analysis was performed using the markers D16S283 and D16S291 flanking the PKD1 gene. The markers were informative in the family and a strongly negative lod score allowed exclusion of this locus as a candidate. The possibility of this family falling into the category of PKD2 disease was considered.

When a second relative developed renal cell carcinoma, a diagnosis of polycystic disease became less likely and linkage was sought to the VHL gene locus on chromosome 3. The
Disease was linked to the marker D3S1038 in this family without recombination with a maximum lod score of 2.90. Four clinically normal individuals aged 1, 7, 15 and 24 years respectively were found to carry the disease allele. Annual screening has continued to show no clinical evidence of disease. In addition eight at-risk individuals were found not to carry the disease allele.

Mutation analysis of the VHL gene is currently being performed (Dr E. R. Maher, Cambridge, UK); however, the mutation in this family remains elusive. Once this is identified it will allow a more accurate prediction of carrier status for individual family members.

Discussion

ADPKD is the commonest renal cystic disease with a prevalence of 1:800 to 1:1000, and accounts for 10% of patients on renal replacement therapy. The family described is a clear example of the diagnostic difficulty that can arise in families presenting with cystic kidney disease. ADPKD is usually diagnosed in patients with chronic renal failure or hypertension on ultrasound by the presence of multiple cysts in both kidneys. The proband fulfilled these diagnostic criteria and with the positive family history of cystic kidney disease a fairly confident diagnosis of ADPKD had initially been made. However, atypical features in this family that suggested a different diagnosis were the presence of intracystic calcification, the development of renal cell carcinoma in two family members, and the presence of pancreatic cysts. Renal cell carcinoma (RCC) is unusual in ADPKD [10].

Genetic linkage analysis was undertaken initially in this family to confirm the clinical diagnosis. The PKD1 locus was excluded by analysis of flanking microsatellites. Five to 15% of patients with ADPKD, however, are unlinked to PKD1 and it was felt that this family may fall into that category. When a second family member developed RCC the alternative diagnosis of VHL was considered. This was confirmed using the close-flanking marker D3S1038. Mutation analysis has as yet failed to identify the precise mutation in the VHL gene. This is currently the case in 20–25% of families with VHL disease.

The accurate diagnosis of VHL and not ADPKD in this family has very important consequences. The high incidence of malignancy in VHL makes screening of family members obligatory. It is currently recommended that individuals at risk for VHL disease undergo regular screening with annual fluorescein angiography, annual renal ultrasound, and CT scan or MRI of the brain and abdominal CT scan at 3-yearly intervals [2]. Genetic linkage analysis, in addition to confirming the diagnosis, also allows proper targeting of this screening to family members who carry the disease allele, leading to a significant saving of resources. The marker D3S1038 is a close marker but it is not intragenic and there is still a small chance of recombination between the disease and this marker. Risk prediction in this family is therefore not absolute but rather a function of the recombination fraction between the disease and the marker. Twelve at-risk individuals were identified who do not carry the disease allele, and screening in this group can be greatly reduced. Four asymptomatic individuals have been shown to carry the disease allele and this group are being monitored closely. Indeed, one patient (III 11) has recently been shown to have developed a cerebellar haemangioblastoma.

Renal cell carcinoma in VHL disease is associated with a high mortality as the tumours are often advanced at the time of presentation. The tumours are commonly bilateral and occur at a younger age than sporadic tumours [11]. Screening and the early identification of RCC may improve prognosis by permitting nephron-sparing surgery, maintaining renal function, and avoiding the complications of renal replacement [12–14]. Successful renal transplantation has been described in anephric VHL patients following bilateral nephrectomy, however, a significant proportion developed metastatic disease post transplantation [15]. The risk of immunosuppression promoting tumour formation in other tissues must also be considered.

VHL disease and ADPKD can therefore have identical clinical presentations. Features in common may include multiple urinary tract infections, hypertension, radiological evidence of renal cysts and rarely pancreatic cysts and chronic renal failure. Subarachnoid haemorrhage (as a rare presentation of haemangioblastoma in VHL [16] or intracranial aneurysms in ADPKD) may also occur in both conditions. Of particular note in this family is the progression of the renal disease in the proband to end-stage requiring renal replacement therapy. This occurred prior to nephrectomy for RCC and to our knowledge has only been once previously described [17].

In conclusion, ADPKD is clearly the leading cause of inherited cystic kidney disease, but alternative diagnoses such as von Hippel–Lindau disease and tuberous sclerosis need to be considered in atypical cases. VHL disease should be considered in any patient with polycystic kidneys who develops renal cell carcinoma [18,19].

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