
Editorial Comments

Von Hippel-Lindau syndrome: a rare syndrome as the clue for the molecular basis of common renal disorders

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Multiple renal cysts, bilateral renal cell carcinomas, hypertension (as a result of pheochromocytomas), retinal angiomasis, and CNS hemangioblastomas are the principal features of Von Hippel-Lindau syndrome [1]. Nephrologists will therefore be confronted with this disease. Although it is regarded a rare disorder, its importance reaches far beyond the relatively modest number of affected individuals. Systematic studies of the Von Hippel-Lindau syndrome have provided far reaching insight into the molecular genetics of renal disease.

Clinical studies of patients with Von Hippel-Lindau syndrome are a rewarding exercise, since the lesions, though rare in absolute terms, are often life-threatening if left untreated, yet curable if detected in time [2]. The key to the detection of such asymptomatic lesions is an understanding of the genetics of the disease. Indeed screening patients with candidate lesions and relatives of affected patients is very effective.

We were the first to provide an accurate estimate of the prevalence of Von Hippel-Lindau syndrome, i.e. 1:39,000 to 1:53,000 in the general population, figures which have been confirmed subsequently by others [3]. Based on these figures, it is reasonable to expect that in large European countries like Germany, Great Britain, France, and Spain there are approximately 2000 patients and another 6000 patients in the USA who have the disease.

The spectrum of renal disease in Von Hippel-Lindau syndrome

Renal involvement in Von Hippel-Lindau syndrome is characterized by a broad spectrum of manifestations. Multiple and bilateral cysts are a frequent finding and present in about 30% of affected individuals [1]. Large and small cysts are present in the same patient. Multiple cysts all over the kidney may mimick autosomal-dominant polycystic kidney disease. Renal cysts in Von Hippel-Lindau syndrome are mostly asymptomatic. Large single cysts may be the cause of abdominal discomfort and occasionally of considerable pain. In contrast to autosomal-dominant polycystic kidney disease, progressive renal insufficiency and renal hypertension have not been reported to date in the Von Hippel-Lindau syndrome.

The second renal manifestation of Von Hippel-Lindau syndrome is cancer. Histologically these are always renal cell carcinomas. Symptoms are similar to sporadic renal cell carcinoma and clinical findings may be indistinguishable from sporadic renal cell carcinoma [1]. A typical feature, however, is the coexistence of tumours with bilateral cysts, and the tumours may occur in a multicocular fashion. The clinical course is dominated by metastases to the liver, lungs and bones; the central nervous system is rarely affected [4]. The survival of patients with Von Hippel-Lindau syndrome depends to a large extent on the occurrence of renal cell carcinoma which is the cause of death in 13 to 50 percent of patients [2].

Only few patients with Von Hippel-Lindau syndrome require renal replacement therapy; this is the result of renal surgery for renal cell carcinoma with eventual bilateral nephrectomy. Renal transplantation has been performed only in few of these patients. Long term follow-up in these rare patients did not reveal cysts or tumours in the transplant. It is of interest that immunosuppressive therapy did not influence symptoms or progression of extrarenal manifestations in Von Hippel-Lindau syndrome.

There is still some debate as to the optimum management of the renal lesions in Von Hippel-Lindau syndrome. Therapeutic nihilists recommend follow-up investigation only, activists recommend bilateral nephrectomy. We feel that as long as only cysts are present, regular observation is sufficient. It is important to make balanced decisions once solid masses are present. Conservative surgery is now generally recommended in an effort to avoid the need for chronic dialysis. Tumour enucleation is the procedure of choice even if multiple tumours are present.

Hypertension in Von Hippel-Lindau syndrome is caused by pheochromocytoma

Pheochromocytoma is a classical manifestation of the Von Hippel-Lindau syndrome and is found in about 15% of affected individuals [1]. It is peculiar that
pheochromocytoma is a dominating lesion in some families and absent in others [3]. It is of particular interest that a patient with isolated pheochromocytoma is at risk of having Von Hippel-Lindau syndrome. It is difficult to exclude VHL in this situation because there are no known blood markers for Von Hippel-Lindau syndrome. To resolve this issue we examined the central nervous system (using gadolinium enhanced magnetic resonance imaging), the eyes (using retinoscopy), the kidneys and the pancreas (using computerized tomography), and the epididymis (using ultrasound) in an extensive clinical study including 82 patients. We achieved complete ascertainment in all cases of isolated pheochromocytoma which had been seen over a 22.5 year period in the circumscribed area of southern Baden in South West Germany [5].

The conclusion of this study was that in unselected patients with pheochromocytoma the risk of having Von Hippel-Lindau syndrome is 19.5%. Useful additional information was obtained. Although 38% of these patients had a positive family history for Von Hippel-Lindau syndrome, the propositi presented with isolated pheochromocytoma. Significant differences between sporadic and Von Hippel-Lindau syndrome-associated pheochromocytoma were found. Pheochromocytoma occurring in patients with Von Hippel-Lindau syndrome were less frequently malignant (0% versus 11%) but more often multifocal (44% versus 8%).

An important question is the accuracy of modern diagnostic methods to identify or rule out pheochromocytoma. We initiated a prospective study comparing the diagnostic values of plasma and 24 h urine catecholamine assays, radiological imaging procedures, CT scanning, MR scanning, and MIBG (metaiodobenzylguanidine) scintigraphy. In the large population studied, 42 unsuspected tumours were detected in 36 (i.e. 46%) of the subjects examined. Abdominal sonography and vanillylmandelic acid assays in 24 h urine, both frequently used as the only methods for excluding pheochromocytoma, turned out to have insufficient sensitivity (63 and 40%, respectively). The best methods were MR imaging without contrast medium and MIBG scintigraphy (sensitivity 95% each) followed by 24 h urine norepinephrine (86%).

Genetics of Von Hippel-Lindau syndrome

There has been enormous progress recently in this field because large well-documented pedigrees (including our own series) have been made available to the geneticists.

Von Hippel-Lindau syndrome is inherited in an autosomal dominant fashion. The penetrance is high, but not complete by the age of 40. Both sexes are affected equally regarding the major complications (eye, CNS, kidneys, adrenal gland, pancreas). In our series the youngest symptomatic patient was 4 and the oldest 78 years old. The VHL (Von Hippel-Lindau syndrome) gene localized on the short arm of chromosome 3 (3p25-26) has recently been identified [7]. The large spectrum of germline mutations comprises single base (point) mutations, short and large deletions and rearrangements. The detection of a germline mutation provides confirmation of the diagnosis. This facilitates clinical management of families with Von Hippel-Lindau syndrome, since screening and follow-up investigations can be restricted to gene carriers. Phenotype-genotype correlations of different families showed that families with pheochromocytoma frequently have point mutations (missense mutations), whereas most families with renal cell carcinoma have deletions within the VHL gene [8].

Two aspects of the genetics of Von Hippel-Lindau syndrome are of special and general interest: (i) The Von Hippel-Lindau syndrome can be caused by a number of different germline mutations (similar to Alport syndrome). Various phenotypes are correlated to specific mutations (genotypes) within the VHL gene. (ii) Mutations within the VHL gene have been detected in approximately 30% of sporadic renal cell carcinomas [9,10]. It will be of interest to elucidate the role of the VHL gene in the pathogenesis of renal cell carcinoma in general.

It is obvious from the above that Von Hippel-Lindau syndrome and the VHL gene carry much greater importance than has been appreciated previously.

References