The kidney in tuberous sclerosis: manifestations and molecular genetic mechanisms

Julian R. Sampson

Institute of Medical Genetics, University of Wales College of Medicine, University Hospital of Wales, Cardiff CF4 4XN, UK

Abstract. Renal involvement is common in tuberous sclerosis. Angiomyolipomas and cysts are found in ~50 and 30% of patients respectively, and often occur together. Tuberous sclerosis also appears to be associated with a small but increased risk of renal cell carcinoma. Recent studies have begun to elucidate the molecular genetic mechanisms underlying the renal manifestations of this systemic autosomal dominant disorder.

Key words: kidney; tuberous sclerosis

Introduction

Tuberous sclerosis is an autosomal dominant trait characterized by the development of hamartomas in many organs, particularly the brain, skin, heart and kidneys. Two tuberous sclerosis associated genes, TSC1 and TSC2, have been localized to chromosomes 9 and 16 respectively [1,2] and the latter has been cloned [3]. The phenotypes associated with mutations at the TSC1 and TSC2 loci appear indistinguishable in the majority of cases [4]. The expression of both genes varies markedly, within as well as between affected families. Mental retardation occurs in a minority of patients [5] and a variety of complications, including those due to renal involvement, are being recognized in an increasing proportion of otherwise mildly affected individuals. This article reviews the renal manifestations of tuberous sclerosis and discusses the findings of recent molecular genetic studies which have provided insights into the aetiological mechanisms involved.

Angiomyolipoma

Angiomyolipomas are non-encapsulated benign tumours comprising variable proportions of fat containing cells, smooth muscle cells (often with cellular atypia) and arterial vessels whose thickened walls lack normal elastic tissue. Solitary angiomyolipoma are seen in the general population, especially among older women [6]. In tuberous sclerosis they are usually multiple and bilateral, and their prevalence is age-related [7,8]. Most lesions of more than a few millimetres are easily recognized on renal ultrasound scan because of their high fat content and, using this investigation, angiomyolipomas can be demonstrated in 50% of adults with tuberous sclerosis [8,9].

Haemorrhage is the major complication attributable to these highly vascular tumours. There is evidence that the risk of spontaneous haemorrhage is related to angiomyolipoma size [10]. Surgery [10] or embolization [11] may be required for active haemorrhage but the place of prophylactic intervention remains controversial. Exceptionally, massive bilateral renal involvement may result in progression to end-stage renal failure [12], but functional renal impairment is probably more frequently associated with cystic disease [13].

Angiomyolipoma may extend into the renal vein and may be found in lymph nodes [14], but the mechanisms underlying such multifocal disease have not been elucidated and progressive metastatic disease has not been reported. A small proportion of patients, almost exclusively female, develop an unusual combination of marked angiomyolipomatous involvement of the kidneys and lung disease with the characteristics of lymphangiomyomatosis [15].

Despite the mixture of cell types, angiomyolipomas appear to be clonal in origin. Studies of angiomyolipomas indicate that a 'two-hit' genetic process underlies their development. Each tuberous sclerosis patient already carries a constitutional mutation affecting one allele of either the TSC1 or TSC2 gene. Evidence for a somatic mutation affecting the second allele comes from the observation of 'loss of heterozygosity' (LOH) in angiomyolipomas. LOH has been documented by parallel assay of polymorphic genetic markers in normal tissue (e.g. blood) and angiomyolipomatous tissue. Reduction from constitutional
Renal cysts

Renal cysts are found in ~30% of patients with tuberous sclerosis [8]. They are usually multiple and bilateral, but both size and number of cysts vary markedly. In many patients cysts and angiomyolipomas occur together and are scattered throughout otherwise normal renal parenchyma. In a minority of cases cysts alone are seen. Cysts may arise in all parts of the nephron and glomerular cysts are occasionally prominent [20]. The epithelial lining usually consists of large, eosinophilic cells with large hyperchromatic nuclei. Mitotic activity is often increased. The epithelium may become piled-up with multiple layers of cells and intratubular masses may form [20], suggesting luminal obstruction as one possible mechanism of cyst formation. The histopathological features of the cystic epithelium are thought to be unique to tuberous sclerosis.

Renal cystic disease remains asymptomatic in the majority of tuberous sclerosis patients and functional renal impairment occurs only rarely. End-stage renal disease has been reported both in patients with renal cysts alone [21] and in those with coexisting cysts and angiomyolipomas [12]. Patients reaching end-stage renal disease have been successfully treated by dialysis and by renal transplantation [22].

Occasionally, severe polycystic kidney disease is an early feature of tuberous sclerosis, being detected within the first few months of life [23,24]. Other features of tuberous sclerosis are not always clinically apparent in early infancy and in such cases initial diagnoses of early-onset autosomal dominant polycystic kidney disease or autosomal recessive polycystic kidney disease have often required later revision [24,25].

The TSC2 gene at chromosome 16p13.3 lies immediately adjacent to the major gene for autosomal dominant polycystic kidney disease, PKD1; the 3’ ends of the genes are separated by only a few hundred base pairs of DNA [26 and unpublished data]. Deletion mutations involving both genes have been identified in six patients with tuberous sclerosis who had severe polycystic kidney disease recognized at or shortly after birth [21]. The deletions appeared to inactivate one homologue of the PKD1 gene (in some cases the whole gene was deleted). This is in contrast with the non-inactivating PKD1 mutations which have been reported in patients with autosomal dominant polycystic kidney disease [26–28]. It is not yet clear whether the severity of cystic disease in the reported cases with deletion of TSC2 and PKD1 reflects the combined mutation of both genes or the nature of the PKD1 mutation alone. Further study is required to establish the role of the PKD1 gene in renal cystogenesis in tuberous sclerosis and the characteristics of renal cystic disease in cases both with and without PKD1 gene involvement require further delineation.

Renal cell carcinoma

Predisposition to renal cell carcinoma in tuberous sclerosis is suggested by early onset and frequent bilaterality in >20 cases reported in the literature. In a smaller number of reports histological features suggestive of oncocytoma and sarcoma have been noted. Histopathological differentiation of these tumours from angiomyolipomas can be problematic [29] and it is likely that, in some cases, they have been diagnosed in error. Details of long-term outcome for tuberous sclerosis patients with renal cell carcinoma are unavailable in most cases; however, in at least three reports death from metastatic renal cell carcinoma has been documented [30–32]. Immunocytochemical staining with the monoclonal antibody HMB-45 has been suggested as characteristic of angiomyolipomas but not renal cell carcinomas or sarcomas [33,34]. However, studies showing that biologically aggressive renal tumours in tuberous sclerosis patients are consistently HMB-45 negative need to be completed before the marker can be used as a guide to management in this specific situation.

Molecular genetic evidence to support a role for the TSC2 gene in the aetiology of renal cell carcinoma comes from an animal model, the Eker rat. Autosomal dominant transmission of predisposition to multifocal renal tumours has been recognized in this strain since 1961 [35]. The tumours have the histopathological appearance of renal cell carcinomas, although they do not appear to metastasize [35,36]. Other tumours, including pituitary adenoma, splenic haemangioma and uterine leiomyoma, are also seen [36]. After discovery of the TSC2 gene in the aetiology of renal cell carcinoma, the Eker rat model provided an animal model of renal cell carcinoma, and TSC2 gene expression was upregulated in renal tumours from the Eker rat [37,38]. Analysis of spontaneously arising renal tumours from the Eker rat has revealed loss of heterozygosity in the TSC2 gene region [38], indicating that the tumours arise by a ‘two-hit’ process analogous to that in angiomyolipomas in patients with tuberous sclerosis. Multifocal renal cell carcinoma has also been reported in two sisters from a chromosome 9-linked (TSC1) family, suggesting a similar role for the TSC1 gene in renal cell carcinogenesis [39]. However, no animal model for TSC1 has been described. Further
work is required to establish the aetiological links between the different types of renal tumour associated with mutations of the TSC genes.

Discussion

Although renal involvement is common in patients with tuberous sclerosis, there are few data on the natural history of the various disease manifestations. The overall importance of renal disease in tuberous sclerosis was emphasized by the findings of a recent study of mortality among tuberous sclerosis patients. Renal complications were second only to those of the central nervous system as a cause of tuberous sclerosis-related death [40].

In the short term, cross-sectional studies should provide more accurate data on the prevalence of renal complications of tuberous sclerosis, but longitudinal studies are required if the place of surveillance and prophylactic intervention are to be adequately assessed. Further understanding of the mechanisms underlying the development of renal cysts, angiomyolipomas and renal cell carcinomas will be facilitated by the characterization of the TSC1 and TSC2 genes. The knowledge gained is likely to be of relevance to both tuberous sclerosis-associated lesions and their sporadic counterparts.

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References


J. R. Sampson


