Clinical developments in polycystic kidney disease

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Introduction

The change in our perspective of autosomal dominant polycystic kidney disease (ADPKD) over the last decade has been impressive; and indeed the recent description of the gene sequence for type 1 ADPKD and putative structure of the protein polycystin highlights the rate of change [1,2].

ADPKD and pregnancy

Advances in clinical management of the condition have been less dramatic than knowledge of the genetics, but nonetheless significant. There is now a good description of the natural history of pregnancy in affected women [3]. The significant role of hypertension is emphasized. New or worsening hypertension, pre-eclampsia and oedema all occur more frequently in affected women. Perinatal mortality and prematurity also tend to be higher in the affected group of mothers with hypertension. Nonetheless, patients who are hypertensive prior to pregnancy are likely to have hypertension during pregnancy, but interestingly, normotensive affected women who develop hypertension during pregnancy are more likely to develop chronic hypertension after delivery. The outcome of pregnancy in normotensive affected women is no different from unaffected controls. Renal function is however less likely to be adequately controlled, mothers can be reassured about the adequacy of intervention and the future status of other family members improves, an increasing number of cases are being confirmed as ADPKD in young children usually present with large kidneys. The presence of renal cysts in neonates and young children tends to result in a diagnosis of autosomal recessive disease. However, as knowledge of the affected status of other family members improves, an increasing number of cases are being confirmed as early onset autosomal dominant disease. These very young children usually present with large kidneys.

References


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and/or hypertension, or as a result of identification by ultrasound screening during the pregnancy [4]. Rapid decline in renal function is not inevitable but close monitoring and early treatment of hypertension is important. The clinician must also however be aware of the wide range of syndromes in children and young adults in which polycystic kidneys are but one of several related complications, for example, in tuberous sclerosis and Von Hippel–Lindau disorder. This is particularly important for patients with tuberous sclerosis who may have cystic kidney disease as a feature of the condition, or who may have ADPKD as a consequence of mutations involving both the TSC2 and adjacent PKD1 gene on chromosome 16 [5].

Blood pressure control—impact on LVH and progression

The rationale for early intervention to treat elevated blood pressure in all affected patients is becoming better established, being justified both on the basis of inhibiting development of cardiovascular disease and possibly also the decline in renal function. Increases in left ventricular mass index are evident in affected adolescents with only mild degrees of hypertension, perhaps as a result of loss of diurnal variation and increase of nocturnal blood pressure [6]. Increases in left ventricular mass index are also associated with enhanced cardiovascular morbidity later in life [7] so that prevention of an increase in LV mass index is a valuable aim. As yet there is no confirmatory evidence that the rate of decline of renal function is influenced by good blood pressure control, indeed results recently reported are disappointing. Two hundred patients with ADPKD were studied as part of the larger Modification of Diet in Renal Disease Study Group [8]. Separate analysis of this group showed that in patients with a glomerular filtration of 25–35 ml/min per 1.73 m², neither a low dietary protein intake nor low target blood pressure (mean BP <92 mmHg in patients 18–60 years, <98 mmHg in older patients) provided any significant benefit by reducing the rate of decline of renal function. If anything, patients with a lower glomerular filtration rate (13–24 ml/min per 1.73 m²) had a more rapid decline, with very low blood pressure control. However, the group for comparison with 'normal blood pressure control' had a mean arterial pressure of <107 mmHg in patients 18–60 years or <113 mmHg for older patients. This still represents effective blood pressure control, and it is important not to extrapolate from the data to conclude that blood pressure control is not of importance in ADPKD. Moreover, all of the patients had significant renal impairment, and the same findings may well not apply to patients with well-preserved renal function. Recent data would suggest that effective blood pressure control does delay the onset of renal failure [9] but more data is clearly required, particularly of the results of studies in patients early in the course of the disease.

Cerebral aneurysms in ADPKD

Rupture of a cerebral aneurysm is a catastrophe for any patient, and early detection and treatment of asymptomatic aneurysms is clearly desirable. As long as carotid angiography remained the only effective method of studying the cerebral circulation, screening was not a valid option. Widespread availability of non-invasive imaging methods such as magnetic resonance angiography (MRA) has changed the situation. The risk of suffering from a ruptured cerebral aneurysm for an individual with ADPKD is very small and there is therefore considerable reservation about routinely screening all ADPKD patients with MRA [10]. However, the demonstration of clustering of aneurysms in some ADPKD families suggests that the prevalence of unruptured aneurysms in these families is approximately 10% [11]. Screening of the family of patients with known aneurysms or subarachnoid haemorrhage with MRA is therefore important. Surgical intervention with clipping of aneurysms greater than 5 mm in diameter is likely to be the treatment of choice. Follow-up screening by MRA of those patients who have already suffered from a ruptured cerebral aneurysm or who have had a very small aneurysm detected previously is also important. Finally, persistent headache in any ADPKD patient probably warrants an MRA scan.

The interface between nephrologist and geneticist

The interface between the clinician and geneticist is likely to be increasingly important in the management of ADPKD. Definition of type I (linked to chromosome 16) and type II (linked to chromosome 4) and other families unlinked to either of these loci will improve information on prognosis. The rate of deterioration of renal function in patients unlinked to chromosome 16 appears to be significantly slower than in type I [12], with many patients not reaching end-stage renal failure during a normal life span. A clearer classification of these 'unlinked families' to those with linkage to the chromosome 4 locus should help to improve the understanding of the natural history of type II disease, and also the significance of the remaining families unlinked to either chromosome 4 or 16 [13]. As the specific mutations on chromosome 16 are identified correlation with clinical features will be possible and perhaps explanations will be found for the substantial phenotypic variation that is so characteristic.

The informed patient

Initially the major impact of all this is likely to be an increased demand by patients and their families for better information about polycystic kidney disease. It is important for patients with type II disease to know of their relatively better prognosis than those with type I. Issues such as the pros and cons of early
diagnosis by abdominal ultrasound or screening for cerebral aneurysms are complex. Patients will expect clinicians to take more time to explain to them the complexities of ADPKD as part of their treatment, so that they are in a position to make rational choices about different aspects of their own treatment. Given the high incidence of ADPKD, the impact of this on clinical workload is not to be underestimated.

References


Oral phosphorus binders without aluminium and calcium—a pipe-dream?

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Introduction

Control of hyperphosphataemia is one of the most difficult problems for the clinical nephrologist. None of the current modalities of treatment is entirely satisfactory. In this context the communication of Spengler et al. in this issue [1] is of particular note.

Why is control of serum phosphate important?

There are several reasons why hyperphosphataemia should be rigorously avoided in the patient with preterminal renal failure, and particularly in the patient on renal replacement therapy. Hyperphosphataemia predisposes to extraosseous calcifications, a problem which has diminished in frequency, but has by no means disappeared. While the role of phosphate in the genesis of secondary hyperparathyroidism in incipient renal failure is still controversial, there is no doubt about the important role that hyperphosphataemia plays in aggravating and promoting hyperparathyroidism in terminal renal failure [2]. It is currently unclear whether these effects are indirect or, as suggested by animal experiments [3,4], whether phosphate directly stimulates parathyroid cells.

Apart from these classical complications it has recently become apparent that many dialysis patients develop aortic valve and mitral valve calcification, calcification of the annulus [5,6] and particularly coronary artery calcification. In a recent study (in preparation) we noted that coronary plaques of dialysis patients were more heavily calcified than those of non-uremic patients. This may for instance be one explanation why coronary artery stenosis recurs so frequently after PTCA.

How can hyperphosphatemia be avoided?

Historically, calcium carbonate was used as early as 1969 [7]. When Clarkson et al. [8] documented that