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Review

Long-Term Outcome of Children with Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT): an Adult Perspective

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Abstract

Paediatric nephrologists know that worldwide 'congenital abnormalities of the kidney and urinary tract' (CAKUT) accounts for around 50% of renal failure and other, familial diseases account for another 20%. Adult nephrologists probably do not know that that this generally remains true up to 40-50 years of age. From a review of the current world literature, the majority of children with renal failure are male and median is 61% (range 51-74%); the diagnosis of CAKUT is made in 51%, and the median total of CAKUT plus hereditary disease is 67%. Progressive renal failure will occur when the final GFR is below 40 ml/min/1.73m2, and is always associated with increasing proteinuria. Angiotensin-converting enzyme (ACE) inhibitors lower blood pressure and reduce proteinuria in children. The evidence that they significantly slow renal failure in children is not yet established, whereas in adults ACEI do slow renal failure in CAKUT. There is no evidence that renal outcome is worse when the CAKUT is associated with bladder failure.

Keywords: CAKUT, reflux nephropathy, proteinuria, abnormal bladder function, angiotensin converting enzyme inhibitors, outcome

Introduction

The scope of this review and the key teaching points can be summarised as:
Paediatric nephrologists know that worldwide 'congenital abnormalities of the kidney and urinary tract' (CAKUT) account for around 50% of renal failure and other, familial diseases account for another 20% (together 70%).
Paediatric nephrologists accept that conditions referred to by the synonyms primary vesico-ureteric reflux, reflux nephropathy, chronic pyelonephritis, chronic atrophic pyelonephritis, are all part of the family of 'primary renal dysplasia' (including synonyms - hypoplasia, adysplasia, hypodysplasia). And that urinary tract infection is not the primary issue.
Paediatricians know everything about the outcome of their patients up to around 14 years of age; while adult nephrologists know everything about their patients from around 16 years (and little before).
Progressive renal failure in CAKUT is a consequence of hyper-filtration in the remnant kidneys. (And therefore similar to any other progressive glomerular disease such as diabetes).
ACE inhibitors lower blood pressure and reduce proteinuria in children – but the evidence that they significantly slow renal failure is not yet established. Whereas in adults ACEI do slow renal failure in CAKUT.
There is no evidence that outcome is worse when the CAKUT is associated with bladder failure. Or, conversely, no evidence that bladder dysfunction is the cause of progressive renal failure in children with congenital outflow obstruction (from e.g. posterior urethral valves).

Discussion

CAKUT as a cause of renal failure.

In the Table 1, I review and summarise the current world literature on the Epidemiology of renal failure in children.
Summarising the data from the Table - the median upper age was 16 (range: upper age 12-22 yrs); the median male majority was 61% (51-74%); the median percentage with CAKUT 51%, and the median total of CAKUT plus hereditary disease was 67%.

There are three points to make:
There is a consensus that worldwide 'congenital abnormalities of the kidney and urinary tract' (CAKUT) accounts for around 50% of renal failure and other, familial diseases account for 20% (together 70%).
The inadequacy of diagnosis coding systems – such as the old EDTA system which has 7 forms of 'pyelonephritis' to choose from – coupled with the lack of effort made in reporting to registries (such as USRDS) means that USRDS data and EDTA data massively under-report the true situation.
China seems to be genuinely different, with glomerulonephritis as the major cause of renal failure (this may also be true for Nigeria, i.e. sub-Saharan Africa). There is data reported in the Table from China and Japan that suggests that CAKUT, particularly that associated with bladder outflow obstruction, is much less common than in the West and the latter also seems to apply to Black Africans.

Moving away from the paradigm of chronic infection in the pathogenesis of renal failure.

The idea that 'scarring' of the kidneys, leading to irregular asymmetric kidneys, is a primary consequence of reflux and urinary tract infection is no longer tenable. This is reviewed in an accompanying paper. While this new view seems to be generally accepted by paediatricians, I believe that most adult nephrologists have not yet accepted (realised) this.

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Table 1. Epidemiology of Paediatric renal failure by country

Publish year	Reference	Age	Country	number	% Males	Congenital /+ Hereditary
2006	(1)	<22	Poland	469	56%	/ 56%
2005	(2)	<16	UK	845	61%	47 / 67%
2005	(3)	<15	Kuwait	171	73%	67 / 88 %
2005	(4)	<16	Holland	351	56%	38 / 62%
2005	(5)	<15	Bangladesh (CRF)	44	68%	60 / 67%
2004	(6)	<14	China (CRF)	1268	60%	/ **25**%
2003	(7)	<20	Italy (CRF)	1197	67%	58% /
2003	(8)	<19	Serbia (CRF)	48	71%	58 / 75 %
2003	(9)	<18	India (CRF)	305	74%	58 / 66%
2003	(10)	<16	Nigeria (CRF)	45	62%	31 / 31%
2003	(11)		Pakistan	78	65%	47 / 61%
2002	(12)	<20	Japan	582	57%	**38** / 57%
2002	(13)	<13	Jordan	202	56%	47 / 77 %
2002	(14)	<12	Jamaica	34	62%	41% /
2001	(15)	<16	Iran (CRF)	166	57%	54 / 75 %
1999	(16)	<18	Chile	227	51%	56 / 67%
1998	(17)	<21	NAPRTCS (CRF)	1725	67%	60 / 64%
1997	(18)	<16	Sweden (CRF)	118	61%	41 / 68%
1995	(19)	<16	Turkey	459	55%	55 / 56%
1994	(20)	<16	France	127	57%	/ 69%
1990	(21)		Saudi Arabia	100		51 / 69 %
1985	(22)	<16	Germany	623		45 / 64 %
1980	(23)	<18	Miami, USA	81		57 / 59 %
2004		<19	EDTA, EU	3441		32 / 42 %
1999		<20	USRDS, USA	5431		/ 35 %

Legend. *Age*: is the age group in that registry; *Country (CRF):* most reports refer to patients starting dialysis. Some registries include all patients with chronic renal failure [CRF). CRF varies from <30- <60 ml/min/1.73m^2; *Congenital/* : is the percentage of patients with CAKUT. /+ Hereditary is the sum of CAKUT *plus* hereditary disease; Missing values – data not available.

CAKUT as a model for remnant kidney nephropathy

Our detailed knowledge of 'glomerular hyperfiltration' and 'remnant kidney nephropathy' is based on the reproducible experimental model in which rats have five-sixths or more of their renal mass ablated. Following nephrectomy, the 'remnant kidney' initially hypertrophies and hyperfiltrates in an attempt to improve the glomerular filtration rate. Subsequently, over a number of months, the animals develop increasing proteinuria, hypertension and progressive renal failure with a glomerular lesion that is characterised histologically by focal and segmental glomerulosclerosis [24]. It always seemed likely that CAKUT was nature's example of this model and everything we have learnt about the natural history of renal failure in CAKUT supports this (reviewed in ref [25]).

Treatment and natural history – the Adult perspective

Our own experience of CAKUT and review of the adult literature is published in open access format [25]. I will, therefore, only summarise some key points:

In our study of "Renal outcome in adults with renal insufficiency and irregular asymmetric kidneys" we included not only patients with normal bladders and ureters who had *primary* reflux nephropathy, but also those born with congenital bladder outflow (such as PUV) who had *secondary* reflux nephropathy [25]. The latter group had hitherto always been excluded from such reports.

Only 10-20 % of adult patients with primary reflux nephropathy, who reach end-stage renal failure (ESRF), present in childhood. The male to female ratio of adult patients is 1:1. Men present with asymptomatic proteinuria, hypertension and or renal insufficiency. Women present either with hypertension, when starting the contraceptive pill, or during pregnancy with hypertension or pre-eclampsia.

Brod [26] (1956), in Czechoslovakia, was one of the first physicians to publish extensively on 'chronic pyelonephritis' and first pointed out that proteinuria was common in severe cases and that proteinuria in excess of 1.5 g/d had a poor prognosis.

Kincaid-Smith [27] (1978) similarly reported that GFR was unlikely to deteriorate until proteinuria exceeded 1g/d (100 mg/mmol).

Zucchelli [28] (1991) reported that GFR would inevitably deteriorate once the creatinine was in excess of 1.7 mg/dl (150 µmol/l).

Goodship (2000) [29]: found that there was no progression of renal insufficiency if the creatinine did not exceed 90µmol/l.

We reviewed 78 patients with asymmetric irregular kidneys (CAKUT) as a consequence of either primary vesico-ureteric reflux or renal dysplasia (Group 1, n=44), or abnormal bladder function (Group 2, n=34). All patients (median age 24 years) had an estimated GFR (eGFR) <60 ml/min/1.73m^2 with at least 5 years of follow up (median 143 months) [25]. 48 patients received ACEI. At start, mean creatinine was 189 µmol/l, mean eGFR 41

ml/min1.73m^2, mean proteinuria 144 mg/mmol (1.7 g/24 hrs). Of 78 patients, 36 (46%) developed ESRF, but none of 19 with proteinuria less than 50 mg/mmol and only two of 18 patients with eGFR above 50 ml/min did so. Renal outcome between Groups 1 and 2 were similar with no evidence for a difference. A benefit in favour of treatment with ACEI was observed above an eGFR of 40 ml/min. We concluded that the similar outcome of the two groups supports the nephrological nature of progressive renal failure in young men born with abnormal bladders. There is a watershed GFR of 40-50 ml/min at which ACEI treatment can be successful at improving renal outcome. All these findings were consistent with previous studies.

Treatment and natural history – the paediatric perspective

Until recently there was little outcome data on primary reflux nephropathy in children, none on secondary reflux and no outcome studies of the effect of ACEI. This has changed in the last 2-3 years and is reviewed in another accompanying paper.

One recent retrospective single centre review of children treated at Great Ormond Street Hospital in London, should be mentioned, however, and its key results summarised [30].

176 children were reviewed with CRF secondary to renal dysplasia, reflux nephropathy or renal obstruction with at least 5 years of follow-up. The development of renal function could be separated into three time periods: (1) During the first years of life, 82% of the children showed early improvement of their kidney function, which lasted until a median age of 3.2 years (median improvement 6.3 ml/year). (2) From the age of 3.2 years until 11.4 years, 53% of the studied children showed a stable kidney function, whereas in 48%, kidney function immediately started to deteriorate. (3) Around puberty, 43% started deterioration in kidney function, whereas 57% even after puberty showed a stable function. Patients with proteinuria (Ua/Uc >200 mg/mmol) deteriorated faster (-6.5 compared with -1.5 ml/min/1.73m^2 per year) than those with Ua/Uc <50 mg/mmol. Children with more than two febrile UTIs, hypertension or an eGFR at onset of less than 40 ml/min deteriorated faster than the others. Although most children experienced early improvement of kidney function, the further prognosis was related to albuminuria, number of febrile UTIs, eGFR at onset of deterioration, hypertension and puberty.

Conclusions

Although GFR can improve in the first 3 years of life, long-term outcome relates to best GFR. By adulthood, patients with GFR <40 ml/min/1.73m^2 will progress to ESRF.

Even with a GFR of 40-50 ml/min, renal function is stable while there is no proteinuria.

Increasing proteinuria (a rising trajectory of urine protein/creatine ratios) is an indication to start an angiotensin antagonist.

Patients with abnormal bladders do not appear to do worse. If such a patient has deteriorating function *but* no proteinuria they will have a 'non-nephrological' problem. This will usually be progressive scarring from recurrent urinary tract infection or a urological problem with drainage - which will require urgent attention.

Conflict of interest statement. The author declares no conflict of interest.

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