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The small scarred kidney in childhood*

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Abstract. Reflux nephropathy is now a generally accepted term to describe small scarred kidneys discovered during childhood; it recognises the close association between this renal lesion and vesicoureteric reflux (VUR). This paper briefly reviews the pathogenic factors involved in reflux nephropathy and suggests that at least two main mechanisms operate: acquired segmental scarring due to intrarenal reflux and congenital maldevelopment (renal dysplasia). The spectrum of renal changes associated with VUR can be usefully divided on this basis and the opportunity to recognise by fetal ultrasound those renal lesions acquired in utero may further enhance our understanding of the congenital maldevelopment group.

Key words: Vesicoureteric reflux – Intrarenal reflux – Reflux nephropathy – Renal dysplasia

Introduction

Children with small kidneys having irregular outlines and deformed pelvicalyceal systems are a familiar problem in paediatric practice. Recognition of the close association between this type of renal scarring and vesicoureteric reflux (VUR), first described by Hodson and Edwards [1] and amply confirmed by others [2–7], is now enshrined in the term 'reflux nephropathy'.

The mechanisms responsible for the renal damage in reflux nephropathy have been reviewed in this journal [8], when the possible roles of intrauterine renal maldevelopment, functional urinary obstruction, bladder dysfunction and urinary infection in relation to VUR were explored.

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Pathogenic mechanisms

Much of the clinical and experimental work on reflux nephropathy has investigated the development of *segmental* scarring which, right from the original description of Hodson and Edwards [1], has been regarded as the hallmark of this condition.

The phenomenon of intrarenal reflux (IRR) has been regarded as the vital link between VUR and segmental scarring. With retrograde propulsion of urine during detrusor contraction at micturition into the upper urinary tract as a consequence of VUR, the normal pressure gradient between the renal tubules and the renal pelvis is reversed. This allows retrograde flow of urine from the pelvis into the papillary collecting ducts and renal tubules. This process of IRR provides a mechanism whereby any pathogenic organisms that might be present in the bladder urine can gain access to the renal parenchyma and initiate infection and subsequent scar formation (infected reflux-associated scarring) [9]. Roberts et al. [10–14] suggest that ischaemia and reperfusion damage due to the release of superoxide are important pathophysiological events consequent on the introduction of pathogenic organisms into the kidney. Ransley and Risdon [15] have demonstrated experimentally that infected reflux-associated scarring occurs quickly, in the space of only 1–2 weeks, and that such scarring is particularly rapid, severe and extensive when infected reflux is accompanied by urinary obstruction.

It is also possible that in some circumstances the hydrodynamic effects of IRR alone, even in the absence of urinary infection might cause scarring (sterile reflux-associated scarring) [4]. In either event, there is good clinical [3] and experimental [16] evidence associating IRR with subsequent scar formation in the affected segments of the kidney.

IRR does not occur at every renal papilla, but is dictated by the morphology of the papilla concerned [9, 17, 18]. Some papillae, particularly those at the poles of the kidney, tend to be fused compound structures with a flat or concave area cribrosa and open papillary duct orifaces that allow free IRR (refluxing papillae). Others, seen more frequently

in the midzones of the kidney, are simple, conical structures with slit-like papillary duct orifaces opening tangentially to the area cribrosa, that tend to close as the pelvic pressures rises and that do not, therefore, allow IRR (non-refluxing papillae).

Comparing papillary morphology in terms of propensity to IRR in porcine and human kidneys, it has been shown that compound refluxing papillae are less common in humans, and about one-third of the kidneys of human children possess only non-refluxing papillae [17]. However, sustained reflux with an abnormally high bladder pressure can flatten the area cribrosa of an initially non-refluxing papilla, converting its morphology to make it prone to IRR [9].

With regard to sterile reflux-associated scarring, the clinical importance of this mechanism remains controversial. Bailey [4] indicated that segmental scarring in reflux nephropathy is largely a hydrodynamic effect of IRR and that renal infection, although often present, is relevant only in producing symptoms that draw attention to the renal scarring but is not involved in its pathogenesis. Hodson et al. [16] concluded on the basis of their experimental work in the pig, that high pressure VUR and IRR produced segmental scarring both with and without urinary infection, the only difference being that scarring occurred quicker with infection.

In our own initial experiments using Hodson's pig model [9], we were able to produce segmental scarring only in the presence of urinary infection and never when the urine was kept sterile. In these experiments two groups were prepared: (1) animals voiding at normal bladder pressure and (2) animals fitted with urethral rings of a calibre sufficient to raise detrusor pressure during voiding but insufficient to produce upper tract dilatation indicative of sustained urinary tract obstruction. In a subsequent series, however, tighter urethral rings were used to provide a sustained elevation of bladder pressure, to the point of bladder decompensation associated with marked upper tract dilatation [19]. Under these circumstances, rapid and diffuse segmental renal scarring in the absence of urinary infection was achieved. We were nevertheless unwilling to ascribe great clinical significance to this observation because of the highly unphysiological conditions required.

These various clinical and experimental studies do much to explain various perplexing aspects of reflux nephropathy. The IRR mechanism and its relation to papillary morphology clarifies the predominantly polar distribution of the segmental scars, their position directly overlying calyces, their wedged shape and their usually sharp demarcation from adjacent unscarred parenchyma. The calyceal clubbing, that is a familiar radiological feature of the scars, is a result of papillary distortion and subsequent retraction following scar contraction.

The rapidity with which scarring can occur in the presence of VUR and urinary infection probably explains why scarring is usually fully developed when a child is first investigated, since scarring may frequently occur in infancy or early childhood, perhaps with the first significant urinary infection. Newly acquired scars are, nevertheless, sometimes documented clinically but, as Smellie et al. [20] have shown, new scar formation seems to be invariably associated with urinary infection.

Occasionally, particularly in older children and adults, typical segmental renal scarring may be observed in the absence of demonstrable VUR. This is explained by the tendency of VUR to disappear with time. Thus in these patients reflux-associated scarring is presumed to have occurred earlier in life, but VUR has subsequently resolved.

The fact that some children with VUR and repeated urinary infections fail to develop segmental renal scars may be explained by their kidneys lacking papillae with a refluxing morphology, so that with normal voiding pressures they are immune from IRR.

Bladder dysfunction may also be an important factor. We have expressed the view that sterile reflux-associated scarring is of limited clinical relevance, due to the extreme hydrodynamic conditions required to produce it experimentally [19]. However, it is possible that this mechanism might operate, for example, in some infant boys with posterior urethral valves or in some children with a neurogenic bladder or dysfunctional voiding. Nevertheless, in these circumstances complicating urinary tract infections are common, and we have shown the devastating effects of high pressure infected reflux in terms of the associated extensive and severe renal scarring produced [15]. It is probable that scarring is augmented under these circumstances by the transformation of initially non-refluxing to refluxing papillae, rendering further areas of the kidney susceptible to the effects of infected VUR.

VUR and renal growth

It has been suggested that persistent VUR during infancy and childhood interferes with renal growth. Evidence supporting this is usually derived from measurements of the kidneys, (length, area, etc.) based on serial excretory urograms. However, these measurements are difficult to assess, especially in the presence of hydronephrosis or renal scarring [21]. In scarred kidneys small size may be related to the extent of the scarring process; growth of uninvolved parenchyma may be masked by contraction of the scarred areas so that little change in overall size may occur, despite the organ achieving maximum growth potential of its undamaged portions. When scarring is unilateral or unequal on the two sides, compensatory hypertrophy of the normal or less-damaged kidney may further complicate the issue. This has been discussed extensively by Ransley et al. [22] who were unable to show any conclusive effect of VUR on renal growth in the absence of renal scarring.

Developmental mechanisms

The studies described so far have envisaged reflux nephropathy as a largely acquired lesion, the scarring resulting from sterile or infected IRR into a normally developed kidney. Recently, attention has also focused on the effects of VUR in utero on renal development. Anomalous metanephric differentiation (renal dysplasia) is frequently

associated with other congenital malformations or functional abnormalities of the urinary tract, including VUR [23–25]. This has led to a wider concept of urinary tract dysplasia, in which the malformation of the kidney is merely one component.

Mackie and Stephens [26] have proposed a theory of urinary tract dysplasia in which the renal maldevelopment is related to the position of the ureteric oriface; this in turn provides evidence of the point from which the ureteric bud develops. Should this be too far cranially (laterally ectopic within the bladder) or too far caudally (in the bladder neck, urethra or vagina), then growth of the ureteric bud brings it to impinge on the metanephric blastema other than at the normal point of contact so that it will fail to induce normal differentiation. Particularly if the ureteric bud is laterally ectopic, it may produce VUR which is associated with renal parenchymal maldevelopment or dysplasia. On this hypothesis, both VUR and renal dysplasia are separate expressions of a malformed urinary tract. Other workers propose a more direct relationship implying that VUR in utero, particularly if of sufficient severity to produce functional urinary obstruction, may of itself interfere with renal development [27].

Certainly infants with gross VUR, hugely dilated upper tracts and tiny malformed kidneys are a familiar problem, and the evidence that renal damage is largely developmental seems undeniable. It is also entirely possible that superadded acquired renal damage as a result of infected or sterile reflux may occur postnatally.

Clinicopathological correlations

It is clear that the spectrum of renal damage associated with VUR is wider than generally envisaged. At least two fairly distinct populations can be recognised. In the first renal scarring is recognised in childhood, adolescence or adult life. Patients may present with urinary tract infection, hypertension or renal insufficiency. The renal scarring is segmental, overlying clubbed calyces, and the clear presumption is that it is acquired through VUR and IRR of infected urine occurring in initially normally developed kidneys by the mechanisms described here. VUR may be demonstrated radiologically or by isotope cystography, or may have remitted spontaneously.

An important subset of this group are patients with high pressure VUR associated with a neuropathic bladder or sphincter dyssynergia. Such patients may develop severe and extensive segmental scarring associated with urinary infection or possibly with high pressure sterile reflux.

In the second group renal damage is recognised in infancy and VUR tends to be gross and often bilateral. It seems highly likely that at least some of the renal changes represent maldevelopment and occur in utero. The possibility that intrauterine urinary obstruction, which may be transitory, can contribute is suggested by the occasional demonstration of urethral narrowing and detrusor hypertrophy in some affected male infants.

The opportunity now exists for recognising these patients early through the demonstration of hydronephrosis by fetal ultrasound and the subsequent confirmation of VUR in the early postnatal period. Whilst by no means all infants discovered in this way have severe renal impairment, initial studies have provided some interesting insights [28]. VUR tends to be gross and, unlike VUR detected later in life, there is a marked male preponderance of between 2:1 and 5:1 [29, 30]. Decreased renal function, assessed by dimercaptosuccinic acid scintigraphy [30, 31], occurs in about 20% of kidneys, and these tend to be small with smooth outlines rather than segmental scarring. It seems probable that further investigations of patients discovered in this way, by modern imaging techniques and quantitative isotope cystography combined with urodynamics, will further clarify the possible underlying pathogenic mechanisms causing the associated renal damage.

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Ask the expert*

What is the appropriate management, including drug therapy, for epilepsy in a child with a renal transplant?

Key words: Epilepsy – Renal transplant

Anybody can have a fit given sufficient provocation. Provocations to which renal transplant recipients are exposed include: rapid changes of water, electrolytes and arterial pressure; aluminium overload; steroid encephalopathy and the neurotoxicity of cyclosporin A (CyA) itself. These patients should not be regarded as epileptic – the definition of epilepsy including the notion that attacks are largely unprovoked; the management of children in this situation depends primarily upon establishing the cause of their fits. Where the fits are not apparently provoked, referral to a paediatric neurologist is appropriate for review of the type of epilepsy and the level of investigation needed.

Of particular concern to the nephrologist is the interaction between anticonvulsants and immunosuppressants. The major anticonvulsants, carbamazepine, phenytoin, phenobarbitone and primidone, will increase the activity of the hepatic cytochrome P-450 oxygenase system, responsible for the breakdown of both CyA and steroids. This is possibly the reason that the addition of one of these anticonvulsants in a patient on CyA will lead to halving or more of the CyA blood levels. Addition of carbamazepine 200 mg three times a day in one renal transplant recipient caused the CyA level to fall from 346 mg/ml to 64 mg/ml within 3 days. A week later the level had fallen to 37 mg/ml [1]. CyA clearance was shown to increase from 3.8 ml/min per kg to 12 ml/min per kg in one child with a renal transplant whilst on phenobarbitone [2]. Similarly phenytoin was shown to more than halve the CyA levels in six patients despite almost doubling the CyA dosage [3]. The effect persisted for about 1 week after stopping the phenytoin. Phenytoin may also impair the absorption of CyA and in addition has occasionally been reported as causing interstitial nephritis. Sodium valproate appears not to affect CyA levels [4].

Similar interactions have been reported between the major anticonvulsants and systemically administered corticosteroids, dexamethasone, methylprednisolone, prednisolone, prednisone and hydrocortisone. The survival of renal transplants in 75 children on prednisone and azathioprine for immunosuppression, given 60–120 mg phenobarbitone daily, was reduced [5]. Carbamazepine increased the clearance of prednisolone by 75% and of methylprednisolone by 342% in a group of asthmatic children on steroids [6].

Neither sodium valproate nor the benzodiazepines (clobazam, diazepam, clonazepam and nitrazepam) appear to interact with CyA or steroids. No interactions have yet been reported between the newer anticonvulsants (vigabatrin and lamotrigine) and steroids or CyA. Azathioprine does not appear to interact with anticonvulsants.

Where does all this leave us? If the decision to start anticonvulsants has been taken, the situation will be least complicated if sodium valproate is appropriate as a first-line drug, possibly with the addition of either vigabatrin or lamotrigine if the child is having partial fits – with or without secondary generalisation. If the child needs to be on both CyA and a major anticonvulsant (carbamazepine, phenytoin or phenobarbitone), levels of both need to be monitored closely, at least until a stable situation has been reached, to ensure adequate immunosuppression and antiepileptic activity has been obtained. Similarly if a child already on a major anticonvulsant needs a course of steroids, the anticonvulsant levels need monitoring with dose adjustment if necessary. In this situation the steroids should be given at the top end of the dose range with usual careful monitoring for side effects.

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* The editors invite questions for this section