Pediatr Nephrol (2009) 24:227–232
DOI 10.1007/s00467-008-0911-1

EDITORIAL COMMENTARY

Vesicoureteric reflux is not a benign condition

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Received: 25 February 2008 / Revised: 6 May 2008 / Accepted: 7 May 2008 / Published online: 27 June 2008

Abstract Renal parenchymal defects may be congenital, usually associated with dilated vesicoureteric reflux (VUR), or they may appear in previously normal kidneys and be caused by reflux nephropathy due to VUR combined with urinary tract infection (UTI). A piglet model defined that the 70% of children with VUR and vulnerable pyramids would scar rapidly with their first UTI. Because most defects are present at first imaging after a UTI, and from the lack of benefit from apparently reasonable clinical interventions, many now believe that most defects are congenital, their association with VUR being a shared dysplasia rather than causal. Consequently, guidelines now argue for less assiduous management. These conclusions ignore adult human transplant evidence, adult pig studies, and clinical anecdotes, which indicate that scars may develop in infant kidneys quicker than urine culture can confirm the diagnosis, and that reflux nephropathy has no age limit. Its rarity over 4 years suggests that most vulnerable children develop scars before then, despite all medical efforts. I argue that preventing such scarring will require better diagnosis of infant UTI, quicker treatment, reliable imaging of scars and VUR, and subsequent protection until VUR resolves. To make a difference, we need more assiduous management, not less, and cannot afford to consider VUR to be a benign condition.

Keywords Urinary tract infection · Reflux nephropathy · Renal dysplasia · Vesicoureteric reflux · Kidney scars

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Why is there a debate?

Some facts about vesicoureteric reflux (VUR) and kidney parenchymal defects are beyond dispute. First, the vast majority of us (probably about 99%) are born without VUR, and when it does occur it is mostly mild or moderate and resolves during childhood, with very few children having gross VUR and hugely dilated upper tracts. Second, some children have renal parenchymal defects, which are often identified on dimercaptosuccinic acid (DMSA) scans after a urinary tract infection (UTI). Although some kidneys look small, irregular or thinned, most look exactly like normal kidneys, except for having one or more wedge-shaped segments missing. Third, there is an undisputed statistical association between the presence of defects and VUR.

However, there is extensive debate about how these defects occur, especially what roles VUR or UTIs play, if any, in their formation. Sometimes, this debate seems to polarise into two mutually exclusive camps, one that believes that most kidney defects are congenital, and the other that believes that most are acquired as a result of having a UTI in the presence of VUR (reflux nephropathy). The congenital camp explain the association between renal parenchymal defects and reflux by arguing that dysplasia may affect whole "renal units" and cause both the VUR and defects, and they believe that UTIs do not play a primary role. They therefore conclude that there is little value in focussing on the urgent treatment of UTIs, or in imaging for VUR after a UTI, while the reflux nephropathy camp consider these strategies to be of key importance in preventing renal scarring.

I will argue that congenital dysplastic defects and reflux nephropathy both occur. However, I will also argue that relatively few children (usually boys) are born with massive

VUR and defects, and that most children with defects start off with normal kidneys and acquire scars as a result of having a UTI in the presence of more moderate VUR. This will lead to the conclusion that to reduce scarring, we will need to manage their UTIs more, not less, assiduously.

How common is VUR?

The precise incidence of VUR at birth is uncertain, because the invasive nature of cystography precludes our examining healthy babies. However, six studies of infants (and some older children) from a time when such research was considered ethical, showed reflux in only four of 456 (0.9%) healthy subjects, in three of whom the reflux was unilateral [1–6]. More recently, 15 studies (including some extreme outliers [7]) have been reviewed, from which it was concluded that the true figure may be above 1% [8]. Furthermore, the powerful clinical evidence for many cases being dominantly genetically inherited is further supported by sibling concordance rates of 80–100% for monozygotic twins and 35–40% for dizygotic twins [9].

Do congenital dysplastic defects really occur?

Yes, they definitely do. Some children have dysplastic kidneys that are associated with massively dilated, often tortuous, ureters, which usually also have gross VUR [10]. These can occur in the presence of a mechanical obstruction, such as posterior urethral valves, or a functional obstruction, such as a neuropathic bladder, or as part of a more complex pathophysiology, such as the Eagle–Barrett syndrome, but they also occur as an isolated phenomenon, in the presence of gross VUR but an otherwise normal bladder and urethra. Gross-VUR-associated dysplasia is much rarer in girls, though cloacal anomalies can produce a similar pattern.

Animal data provide powerful insights into the impact of intrauterine urological disturbances on the development of renal dysplasia. Even very short periods of intrauterine ureteric obstruction can cause major permanent changes to kidney development, apparently modulated through up-regulation of fetal growth factors [11].

It is common for children with tortuous dilated upper urinary tracts to develop UTIs, because their slow, incomplete, urinary drainage allows small numbers of contaminating bacteria to multiply dramatically (*Escherichia coli* have a generation time of approximately 20 min, which allows one organism to increase to 2,000 in 4 h). Effectively, their problem is having "stagnant" urine. However, when these children do develop UTIs, there is seldom any suggestion that their infections were responsible for causing the renal parenchymal defects, because modern antenatal scanning means that most affected babies are now identified in utero and imaged early in postnatal life, and they are found to have defects before they have had any UTIs. Identifying lesions early in such babies provides a much higher level of proof of their congenital origin than finding them on the first imaging after a child's first recognised UTI, which is often presented as evidence [12].

A common ultrasound pattern seen in babies with congenital dysplasia is one of dilated ureters and calyces, combined with abnormal parenchyme in most or all areas of the kidney, which usually appears bright, often with loss of cortico-medullary differentiation, and sometimes includes cystic changes. Their DMSA scans usually show variable, often asymmetrical, uptake of activity, sometimes with kidneys that are small or appear to be stretched around dilated calyces. This is very different from the typical pattern of reflux nephropathy, which I refer to below, in which otherwise normal-shaped kidneys have sharply delineated segments missing. These distinctions are not always easy to make in individual cases, some babies having congenital dysplasia, but also showing irregularities on DMSA scans.

Does reflux nephropathy really occur?

This undoubtedly occurs too. Our understanding of some of the mechanisms involved in infants are grounded securely in Ransley and Risdon's seminal piglet model [13]. They induced unilateral VUR in piglets, which also have multi-papillate kidneys, by de-roofing the intramural course of one ureter and subsequently inoculating uropathogenic bacteria into the bladders of half the animals. Neither VUR nor a UTI alone had an effect, but whenever both occurred together the kidneys consistently developed segmental scars, with adjacent tissue left unaffected. These predominantly polar scars are indistinguishable morphologically, histologically and on DMSA imaging from the ones seen in children with reflux nephropathy or in adults with pyelonephritis. Furthermore, those authors could postulate how the irregular pattern of damage occurred. During VUR, the segments whose papillary tips were relatively flat-topped (mainly compound pyramids at the poles) allowed urine to enter the renal tubules, whereas intra-renal reflux (IRR) did not happen in the simple cone-shaped ones [14]. Clearly, during a UTI, IRR will allow bacteria to reach those segments of parenchyme. Finally, the authors showed that the resultant damage can occur within just a few days [15]—"the big bang theory".

However, can this elegant animal model be applied to children? While every piglet kidney exposed to VUR and a UTI for a few days develops scarring, this is not so consistent in children. For example, some children with a UTI and bilateral VUR just develop scarring in one kidney. However,

anatomical factors may explain this lower risk. Whereas piglets have many compound papillae [14], children have far fewer, with approximately a quarter of their kidneys having none [16]. The fact that pigs have kidneys that would be vulnerable to extensive scarring, but ureters that never allow reflux, provides an interesting evolutionary perspective. Though there are wide variations in papillary morphology and reflux rates across different mammalian species, none carries a high risk of having both VUR and IRR.

For many years, VUR and renal scarring have been recognised to coexist relatively frequently in children after UTIs [17, 18], and, for some time, it appeared to be a widely held view that most children with kidney scars had sustained them from reflux nephropathy. This was reflected in UTI management guidelines [19], which advocated the use of ultrasound to identify structural abnormalities, DMSA to identify scars, and cystography to detect VUR in certain categories of children. The lack of a complete consistency between the finding of VUR and scarring was accepted, because children could acquire scars and subsequently lose their VUR [20], and because not all human kidneys have vulnerable papillae. Infants were known to be at the highest risk of scarring and were investigated more fully. It was initially thought that children occasionally developed first scars as late as 10 years of age [21], but this was based on intravenous urography evidence, which may fail to identify scars for several years [22], and we later showed in a DMSA-based study that new scarring was unlikely beyond the child's fourth birthday [23]. Although no hypotheses had been published then to explain why an age limit might exist, the many colleagues I polled had all assumed that the kidney parenchyme must become less vulnerable during maturation. Not surprisingly, it became common to treat children with VUR actively up to the age of 4 years, including the use of antibiotic prophylaxis, but not to treat older children.

So why has opinion swung away from reflux nephropathy towards congenital dysplasia?

Despite the well-defined evidence base for reflux nephropathy, many paediatricians now appear to consider congenital dysplasia to be the cause of most parenchymal defects [12]. This belief is reflected throughout the National Institute for Health and Clinical Excellence (NICE) guidelines and in their advice to reduce management activity dramatically from previous standards [24]. However, what has led to this fundamental change in thinking? There are probably several reasons, which I present below, but I do not believe that they withstand careful scrutiny.

First, the conclusion that most parenchymal defects found after UTIs must have been congenital because they are detected at the first imaging is false in two ways. It assumes that kidneys could not scar in the interval between a child's developing UTI symptoms and receiving antibiotics, which is wrong. I have already referred to the "big-bang" nature of scarring in piglets, which challenges this, and later I present evidence that human kidneys can scar equally dramatically fast. The conclusion also assumes that a child's first recognised UTI is actually its first one. Our evidence is that this is a rash assumption. We have shown that, in routine primary care, only a quarter of infants presenting with a UTI are diagnosed [23].

Another commonly employed argument is that VUR does not significantly predispose children to UTI, but simple arithmetic shows that this is false. The VUR rate in newborn babies is of the order of 1% (certainly <2%) [25] and falls with age, whereas VUR is detected in up to one-third of children and half of infants investigated for a symptomatic UTI [26]. If we take rates of 1% and 25%, it would follow that a child with VUR has a 33-times greater risk of developing a UTI. This is predictable from microbiological first principles. After a normal void, the retained urine volume is extremely small, and virtually all contaminating organisms are expelled. By contrast, VUR effectively creates stagnation, because more contaminating bacteria may be retained after voiding, where they will multiply further before the next incomplete void.

Another argument used against actively treating children with UTIs is that neither prophylactic antibiotics nor anti-reflux surgery is effective in preventing scarring [27, 28]. However, there are two reasons why this widely quoted conclusion should be reconsidered. First, these studies are based on intravenous urography imaging. As already mentioned, this may fail to detect kidney scars for years (because, unlike in DMSA scans, they are not primarily identified by loss of function, but by anatomical distortions to the renal outline or calyces) [22]. "New" scars may therefore have been seeded long before the study began. Second, the patient groups are not appropriate to test how to prevent reflux nephropathy in children who may be at risk, but who have not yet had their first UTI. Instead, most are children with VUR who have already had their UTI, scarring, and "big-bang". It is understandable why these studies are quoted, because designing more appropriate ones would be very difficult. For example, studies are needed of infants with VUR identified from screening programmes, rather than after a UTI, who are then followed prospectively by DMSA scanning to compare the protection provided by (a) just careful monitoring and urgent treatment for UTIs, with (b) the addition of prophylactic antibiotics. In a small pilot of that design [29], the only child in our cohort to acquire (extensive) scarring was one who had suffered a prolonged symptomatic UTI and whose parent did not comply with any aspects of management.

Since congenital reflux-associated dysplasia is predominantly a male condition [10], and acquired scarring is predominantly a female one [30], the conclusion that most parenchymal lesions are congenital would predict that more boys would be affected than girls. The opposite is seen in all series.

What is the real age limit to scarring?

Despite there being few reports of DMSA-proven new scars being acquired after the child has reached the age of 4 years, we now know that much older kidneys can scar dramatically quickly when first exposed to VUR and UTI, just as in infants. This is seen in kidney transplant recipients, a pig study, and rare clinical cases. Its implications for understanding native kidney scarring are immense.

Despite our knowing that 40% of transplanted kidneys have wedge-shaped defects on DMSA scans that closely resemble native kidney focal scars, the idea that they could be due to reflux nephropathy was not systematically considered initially. We have since shown that 69% of paediatric transplant recipients exposed to both a UTI and VUR developed new focal lesions, and one that was biopsied confirmed that this was due to pyelonephritic scarring [31]. Most donors were adults, frequently parents, showing that human kidneys do not "mature" out of the risk of scarring, but succumb rapidly on what appears to be their first exposure. The 69% scarring rate is very close to the 73% of human kidneys that have "vulnerable" papillae [16], suggesting that most or all with a UTI, VUR and IRR scarred.

The children whose transplants scarred were not more heavily immunosuppressed or different in any other way. However, to determine whether other non-immunosuppressed adult kidneys might scar on their first exposure to VUR and UTI, we repeated Ransley and Risdon's piglet studies, but in mature sows. All developed reflux nephropathy [32], just like the piglets.

Evidence that native kidney scars begin in children aged over 4 years is much harder to find, but it does happen. For example, a girl found to have VUR after an acute UTI at 3 months of age, who was maintained infection-free up to 4 years, later sustained major scarring following UTIs after the age of 6 years [33].

How quickly do kidneys scar?

For obvious reasons, it is difficult to estimate how long it takes for infants' kidneys to scar in clinical practice, and few will have had a prior DMSA scan that proved that the lesions were genuinely new. Therefore, lessons must be gleaned by careful analysis of every unusual clinical case. Take, for instance, the patient just described, whose UTI at 3 months did not scar what was clearly a vulnerable kidney that scarred later. At 3 months, her UTI caused an acute febrile illness and fit, and she was hospitalised and treated within 12 h, but she waited up to 6 days for treatment of her later damaging infections, pending laboratory confirmation. From similar cases, we believe it is essential to treat within 36 h, to prevent scarring risks, and that delays of 3 days are likely to be too long. Children treated in routine primary care in the north-east of England are unlikely to be treated for UTIs within 3 days [34], except where a nurse-led protocol is in place [35].

Evidence for the dramatic speed of scarring is easier to obtain from kidney transplant recipients. Two girls that acquired new scars in their fathers' kidneys each started with normal findings on their DMSA scans. Each was admitted acutely unwell with a fever lasting just a few hours, was treated immediately, and made a prompt clinical recovery, and yet each acquired extensive scarring sufficient to cause a measurable loss of kidney function [31].

So, why is new scarring so rare after the age of 4 years?

If the initiation of new reflux nephropathy scarring can be demonstrated at any age, why is it so rarely seen after the child's fourth birthday? I have proposed the following mechanisms [25]. First, VUR does greatly increase the risk of acquiring a UTI, especially in girls, whose bladder urine is easily contaminated because of their short urethrae. In 3/4 of infants with a UTI, no diagnosis is made, and they scar. Most of the rest are kept waiting for longer than it takes for scarring to occur while laboratory confirmation is obtained and antibiotics are started, so most of them suffer scarring too. Those general practitioners (GPs) that discard nitrite stick-test-negative samples (as recommended by NICE) will systematically miss approximately 50% of cases [36], and those will also scar. The children with vulnerable kidneys that are later investigated will, of course, have scarring detected at first imaging and will be mislabelled as having had congenital dysplasia.

This depressing hypothesis implies that the way we have managed the condition in children to date has resulted in our identifying kidney damage but has prevented very little. Virtually every child born with VUR and IRR will scar early on, so, by the age of 4 years, almost every child who does not have scarring is one that had never been at risk. New scarring is rare in children over 4 years of age, because there is nobody left who was born at risk and has not already scarred. However, do the figures add up? If this model is correct, we can estimate that approximately 0.7% of people should have kidney scars, since around 1% of

babies have VUR, and, of these, about 70% will also have IRR. In Newcastle we have seen scars in 0.54% of the girls referred to us [37], which is close to the estimate, considering that we must have missed many cases.

Can scarring be prevented, and is it all worthwhile?

Although it is not yet certain that prevention of all acquired renal scarring is possible, there are encouraging signs. In Sweden, infant UTI is managed especially actively, which appears to have significantly reduced the numbers of people developing renal failure [38]. In Newcastle, we have forged a new nurse-led relationship with our GPs, who now use direct-access arrangements to investigate children in whom they have proved UTIs, which has produced dramatic and sustained changes in their clinical activities [35]. They now diagnose UTIs in four-times more infants than they used to and are much more likely to treat immediately on clinical suspicion or after using our day-unit urine microscopy service. Our long-term analyses are not yet complete, but we continue to see many infants who have had a UTI, but been treated promptly, and who have VUR, but have not sustained scars [35]. These children, of course, need to have their kidneys protected from further UTIs until they outgrow their VUR, regardless of age.

Exactly how to improve children's services to attempt to reduce kidney scarring would stimulate much debate, but I believe that positive efforts should be made to do this. Mislabelling most cases of acquired scarring as being congenital will hamper progress by incorrectly removing incentives. Guidelines, such as the NICE ones [24], that are grounded in the concept that little positive can be done to prevent scarring, and that minimise their sequelae, are not helpful. It is hard to see how their advice to rely on urine stick testing in some children, to not refer most children until they have had at least two UTIs, and to rely on ultrasound imaging in most children (thereby missing approximately half the scars) will help, though it will certainly save money in the short term. Proposals need to be developed that investigate children believed to be at the highest risk of scarring, rather than applying rigidly prescriptive guidelines to all, but the evidence that will allow us to identify these groups safely has not yet been established [39]. Registries of children presenting with renal failure contain a high proportion with high-grade VUR (III and above) [40], and follow-up studies of children with high-grade VUR demonstrate a high rate of progression to renal failure in early adult life [41].

The real long-term data are best established not from small follow-up studies, but from our looking at the sequelae in adults, which are out there to be seen. In most kidney transplant programmes, approximately 10% to 15% of transplantations are performed because of pyelonephritis, i.e. the end result of childhood reflux nephropathy. In the north-east of England, one transplantation is performed every month for pyelonephritis, and many more people survive on dialysis, costing £4,000,000 annually [33]. Most of these adults will have had their scarring initiated by an ordinary (i.e. slow) response to their UTI when they were under the age of 4 years. Prevention is always better than cure. We must not lose the opportunity to prevent future renal failure simply because it would involve a more thorough, careful, and probably tedious, approach to looking after large numbers of children with UTIs.

In summary, I believe it may be possible to reduce the rate and extent of renal scarring in future by altering our approach to infant and childhood UTIs, with more prompt diagnosis and treatment and an awareness of the potential hazard that having VUR may cause in this setting. The hope is, that by doing this, we will reduce the numbers of adults with hypertension and renal failure in the next generation of adults.

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